REMARKS

Claims 1-7 and 9-28 were examined in the Office Action dated 9/8/2005. By this communication, claims 3, 21 and 27 have been cancelled, and claims 1-4, 9-11 and 17 have been amended. Claims 1-7, 8-20, 22-26 and 28 are now pending. Applicant requests reconsideration of the pending claims in view of the foregoing amendments and the arguments set forth below.

In the aforementioned Office Action, the examiner maintained his rejection of claims 1, 2, 4-14 [sic, noting that claim 8 had been cancelled], 17-22, 25 and 27-28 as being unpatentable over U.S. Patent No. 5,089,703 to Schoen et al. Applicant had previously explained (in the Amendment/Response filed on 8/17/2005) that the Schoen et al. reference does not teach or suggest axial confinement of ions in an ion channel, a limitation that is present in both of the independent claims (1 and 17) of the present Application. In response to this argument, the examiner stated (at pp. 4-5) that

> 703 [the Schoen et al. patent] teaches the use of ions with stable and unstable
> trajectories and some of the stable trajectories do not exceed the inner dimensions
> of the electrode structure (col. 4, lines 49-67). Therefore, certain ions are
> confined by use of the applied voltages and this confinement is axial confinement
> because these ions stay within the electrode structure.

As understood by Applicant, the Examiner has taken the position that ions traveling along the axis of a quadrupole mass filter that have stable trajectories with transverse dimensions that do not exceed the inner dimensions of the electrode structure can be said to be axially confined. This position is both contradicted by the text of the Schoen et al. reference and inconsistent with the plain meaning of the terms "axially confined" or "confined in the axial direction", as recited in claims 1 and 17.

We note first that the cited section of the Schoen et al. patent states that "[i]ons enter a quadrupole with a finite **axial** (z dimension) velocity and exit after a time, t_{exit}, which depends upon the length of the device and the **axial** velocity [emphasis added]." This teaches that there is no axial confinement of the ions in Schoen et al. because no action is taken to restrict or impede the axial (as distinguished from the radial) movement of the ions; the ions simply enter

one end of the quadrupole, traverse the length of the quadrupole, and emerge from the opposite end.

Applicant further notes that the examiner has failed to give the claim terms "axially confined" and "confined in the axial direction" their plain meaning. It is a settled principle of law that, although the PTO must give claims their broadest reasonable interpretation, this interpretation must be consistent with the one that those skilled in the art would reach. In re Hyatt, 211 F.3d 1367, 1372 (Fed. Cir. 2000); see also M.P.E.P. §2111.01. In the linear ion trap mass spectrometry art to which the claims of the present Application pertain (noting that claims 1 and 17 have been amended to specify a multipole ion trap apparatus having rod electrodes, i.e., a linear ion trap), the term "axial" refers to the central longitudinal axis of the trap structure, and "axially confined" or "confined in the axial direction" means constraining the movement of ions in a direction defined by the central longitudinal trap axis such that the ions remain in the trap and do not emerge from the trap via one of its ends.

Applicant has enclosed herewith a copy of a recent journal article (Douglas et al., "Linear Traps in Mass Spectrometry", Mass Spectrometry Reviews, Vol. 24, pp.1-29 (2005)) to demonstrate the customary meaning of "confined axially." This article is authored by a well-recognized expert in the field of ion trap mass spectrometry (Professor Donald Douglas of the University of British Columbia) and sets forth a summary of the operating theory and performance of linear ion trap instrumentation used for mass spectrometry. In describing the general architecture and operation of conventional linear ion traps, Douglas notes (at page 5, §5) that:

> [a] linear multipole is easily converted into a linear ion trap by applying stopping potentials to electrodes at the entrance and exit. Ions are then **confined radially** by the RF fields, and **axially** by the stopping potentials... In contrast to the 3D ion trap, ions are not **confined axially** by RF potentials [emphasis added].

In other words, the linear ion trap has two distinct modes of confinement: axial confinement (conventionally effected by the application of stopping DC potentials to electrodes at the entrance and exit of the trap), which constrains the movement of ions in a direction defined by the central longitudinal trap axis radial confinement (effected by the generation of RF fields), which limits the movement of ions in the radial dimensions orthogonal to the central longitudinal

axis. Absent axial confinement, ions escape the ends of the linear multipole and hence are not trapped within the multipole interior.

Applicant further offers the Declaration Under 37 C.F.R. §1.132 of John Syka in support of its argument that the terms "axially confined" and "confined in the axial direction" have a plain meaning that does not read on the quadrupole mass filter system described in the Schoen et al. patent. Mr. Syka is the inventor of the subject matter of the present Application, a co-inventor of the subject matter of the Schoen et al. patent, and has considerable expertise in the ion trap mass spectrometry field. In his Declaration, Mr. Syka states (at page 3, §6) that:

> [a]s applied to conventional two-dimensional quadrupole ion trap devices (commonly referred to as "linear ion traps"), "axially" or "axial" refer to the central longitudinal axis of the trap extending between the ends of the device, and "axially confining" ions means constraining the ions' movement in the dimension defined by the central longitudinal axis such that the ions remain within the trap or a section thereof.

and further explains (at page 4, §8) that:

> [t]he '703 Patent [U.S. Patent No. 5,089,703 to Schoen et al.] does not teach or suggest axial confinement of ions in an ion channel, because the motion of ions along the central longitudinal axis is not constrained or impeded by the application of the primary or supplemental RF voltages.

In sum, the independent claims of the Application each contain a limitation of axially confining ions in an ion channel of an ion trap by the application of an oscillating potential. This limitation, as properly construed in accordance with its plain meaning, is not disclosed or suggested by Schoen et al. or the other prior art references of record. Thus, withdrawal of the rejections of independent claims 1 and 17 is believed to be in order and is respectfully requested. Dependent claims 2-7, 8-16, 18-20, 22-26 and 28 all depend directly or indirectly from claim 1 or 17 and inherit all of the limitations thereof, and are submitted to be patentable over the prior art for at least the reasons advanced above in connection with the independent claims.
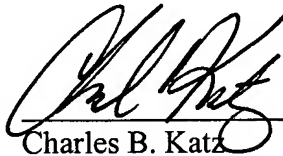
In view of the above discussion, it is submitted that the Application is now in condition for allowance and such favorable action is respectfully requested. The Examiner is invited to

contact the undersigned Applicant's representative by telephone if he believes that doing so will be helpful to resolve any outstanding issues and advance the prosecution of the Application.

The Commissioner is hereby authorized to charge any other fees determined to be due to Deposit Account 50-3267.

Respectfully submitted,

Dated: _20 October 2005_

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LINEAR ION TRAPS IN MASS SPECTROMETRY

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Linear ion traps are finding new applications in many areas of mass spectrometry. In a linear ion trap, ions are confined radially by a two-dimensional (2D) radio frequency (RF) field, and axially by stopping potentials applied to end electrodes. This review focuses on linear ion trap instrumentation. Potentials and ion motion in linear multipole fields and methods of ion trapping, cooling, excitation, and isolation are described. This is followed by a description of various mass discrimination effects that have been reported with linear ion traps. Linear ion traps combined in various ways with three-dimensional (3D) traps, time-of-flight (TOF) mass analyzers, and Fourier transform ion cyclotron resonance mass spectrometers are then given. Linear ion traps can be used as stand alone mass analyzers, and their use for mass analysis by Fourier transforming image currents, by mass selective radial ejection, and by mass selective axial ejection are reviewed. © 2004 Wiley Periodicals, Inc., Mass Spec Rev 24:1–29, 2005

Keywords: *linear multipoles; ion traps; excitation; resonance; space charge; mass analysis*

I. INTRODUCTION

Linear ion traps are rapidly finding new applications in many areas of mass spectrometry. In a linear ion trap, ions are confined radially by a two-dimensional (2D) radio frequency (RF) field, and axially by stopping potentials applied to end electrodes. In comparison to three-dimensional (3D) Paul traps, linear traps have higher injection efficiencies and higher ion storage capacities. Their use is not limited to simply storing ions. They can be combined with other mass analyzers in hybrid instruments and used to isolate ions of selected mass to charge ratios, to perform tandem mass spectrometry experiments, and to study ion-molecule chemistry. Linear traps can operate as stand-alone mass spectrometers. .

One of the first linear traps was constructed by Church (1969) who bent linear quadrupoles into closed circle and racetrack geometries and demonstrated storage of $^3He^+$ and H^+ ions for several minutes. Earlier, Drees & Paul (1964) had described a circular quadrupole. However, it was used to produce and confine a plasma, not to store ions. Deutch et al. (1988) and Waki et al. (1992) described storage of ions in circular quadrupole traps. Beaugrand et al. (1987, 1989) confined ions in the collision cell of a pentaquadrupole mass spectrometer system to study ion-molecule chemistry. At about the same time, Dolnikowski et al. (1988) showed that ions could be trapped in the collision cell of a triple quadrupole system to enhance ion-molecule reactions. This technique was later used by others to study ion-molecule chemistry (Schwartz, Schey, & Cooks, 1990; Chen et al., 1998). Prestage, Dick, & Malecki (1989) described a linear quadrupole trap used to study spectroscopy of stored ions. Following these early works, there has been a rapid growth in the use of linear ion traps in mass spectrometry.

In this review, we attempt to summarize the current status of linear ion trap instrumentation used for mass spectrometry. We have not attempted to cover applications in other fields such as frequency standards (e.g., Prestage, Dick, & Malecki, 1989) or nuclear physics (e.g., Kellerbauer et al., 2002). The review is organized as follows. In Section II, we give a review of potentials and ion motion in linear multipole. fields and a description of methods of ion trapping, cooling, excitation, and isolation. This is followed by a description of mass discrimination effects that have been reported with linear ion traps. Descriptions of linear ion traps combined in various ways with 3D traps, time-of-flight (TOF) mass analyzers, and Fourier transform ion cyclotron resonance mass spectrometers are then given. Linear ion traps can be used as stand alone mass analyzers, and their use for mass analysis by Fourier transforming image currents, by mass selective radial ejection, and by mass selective axial ejection are reviewed. The field is changing rapidly, and new instru-

mentation and applications are appearing. We have attempted to include the work we were aware of up to March 2003.

II. LINEAR MULTIPOLES

A. Multipole Fields

1. Multipole Potentials

Two dimensional multipole fields are well known. Their use for trapping and manipulating ions has been reviewed in detail (Gerlich, 1992). In polar co-ordinates, any 2D electric potential, $\Phi(r,\theta)$, can be expanded in multipoles, φ_N, as

$$\Phi(r, \theta) = [(A\theta + B)(C\ln(r) + D)] + \sum_{N=1}^{\infty} \varphi_N(r, \theta)$$

$$(2.1)$$

The terms $\varphi_N(r,\theta)$ are sometimes referred to as "spatial harmonics" or "circular harmonics" (Smythe, 1939, p. 62) and are given most generally by

$$\varphi_N = (A_N \cos N\theta + B_N \sin N\theta)(C_N r^N + D_N r^{-N}) \quad (2.2)$$

For this review, we are interested in the terms that contain r^N and these can be taken as (Gerlich, 1992)

$$\varphi_N = A_N \phi_N(r, \theta) = A_N \left(\frac{r}{r_0}\right)^2 \cos N\theta \qquad (2.3)$$

Neglecting the first term in Equation 2.1, which describes a constant potential and the potential from a line of charge, in Cartesian co-ordinates a 2D electric potential $\Phi(x,y)$ can be expanded in multipoles, $\phi_N(x,y)$, as

$$\Phi(x, y) = \sum_{N=0}^{\infty} A_N \phi_N(x, y) \qquad (2.4)$$

where A_N is the amplitude of the multipole $\phi_N(x,y)$. The terms $\phi_N(x,y)$ can be derived in analytic form from

$$\phi_N(x, y) = \text{Re}\lfloor (x + iy)^N \rfloor \qquad (2.5)$$

where $\text{Re}[f(\zeta)]$ means the real part of the complex function $f(\zeta)$, $(\zeta = x + iy)$ and $i^2 = -1$ (Smythe, 1939, p. 70; Feynman, Leighton, & Sands, 1963). Analytical expressions for the multipoles in Cartesian co-ordinates are given by Szilagi (1988). The term $\phi_0(x,y) = 1$ represents a potential that is constant (independent of x and y), $\phi_1(x,y)$ represents the potential from two planes of opposite charge (a linear dipole), $\phi_2(x,y)$ is a quadrupole potential, $\phi_3(x,y)$ is a hexapole potential, $\phi_4(x,y)$ is an octopole potential, etc.

The most relevant potentials for this article are the quadrupole potential

$$\phi_2(x, y) = \frac{(x^2 - y^2)}{r_0^2} \qquad (2.6)$$

the hexapole potential

$$\phi_3(x, y) = \frac{(x^3 - 3xy^2)}{r_0^3} \qquad (2.7)$$

and the octopole potential

$$\phi_4(x, y) = \frac{(x^4 - 6x^2y^2 + y^4)}{r_0^4} \qquad (2.8)$$

These potentials describe 2D fields formed by 4, 6, or 8 parallel electrodes, respectively, spaced symmetrically from a central axis by a distance r_0. To produce a pure multipole field of order N, the shapes of the electrodes are determined by the equation $\phi_N(x,y) = $ constant. These shapes are shown by Szabo (1986). In practice, round rods are widely used because they are easier to manufacture. The ratios of round electrode radius, r_e, to field radius, r_0, that give the best approximations to quadrupole, hexapole and octopole fields have been given as $r_e/r_0 = 1.146$, $r_e/r_0 = 0.560828$, and $r_e/r_0 = 0.3739$, respectively (Everdij, Huijser, & Verster, 1973). More recent calculations by Rama Rao & Bhutani (2000, 2001) give the ratios, $r_e/r_0 = 0.5375$, and $r_e/r_0 = 0.355$ for the hexapole and octopole, respectively. The ratio that is optimum for mass analysis with a linear quadrupole is $r_e/r_0 \approx 1.13$. However this does not produce the best approximation to a pure quadrupole field (Douglas & Konenkov, 2002). If a potential $\Psi(t) = \pm(U - V_{RF}\cos\Omega t)$ is applied from alternate electrodes to ground the 2D multipole potential is

$$\Phi(x, y, t) = \phi_N \Psi(t) \qquad (2.9)$$

For example, the quadrupole potential is

$$\phi_2(x, y, t) = \frac{(x^2 - y^2)}{r_0^2}(U - V_{RF}\cos\Omega t) \qquad (2.10)$$

2. Ion Motion in 2D Multipole Fields

The motion of an ion in a 2D multipole field is determined by Newton's law

$$\vec{F} = m\frac{d\vec{v}}{dt} \qquad (2.11)$$

where m is the ion mass, $\vec{v}$, the ion velocity and the force, $\vec{F}$, on a positive ion is

$$\vec{F} = -ze\nabla\phi_N(x, y, t) \qquad (2.12)$$

where z is the number of charges on the ion, and e is the magnitude of the electronic charge. In the absence of collisions, ions move freely along the central axis of the multipole. Motion in the x and y directions, orthogonal to the central axis, is determined by

$$m\frac{d^2x}{dt^2} = -zeA_N\frac{\partial\phi_N(x, y, t)}{\partial x} \quad \text{and}$$

$$m\frac{d^2y}{dt^2} = -zeA_N\frac{\partial\phi_N(x, y, t)}{\partial y} \qquad (2.13)$$

For the pure quadrupole field,

$$-A_2\frac{\partial\phi_2}{\partial x} = \frac{-2x}{r_0^2}(U - V_{RF}\cos\Omega t) \quad \text{and}$$

$$-A_2\frac{\partial\phi_2}{\partial y} = \frac{+2y}{r_0^2}(U - V_{RF}\cos\Omega t) \qquad (2.14)$$

The motion in x does not depend on y and similarly the motion in y does not depend on x. This is an important property of quadrupole fields. For all other higher multipoles, x and y motion are strongly coupled.

3. Ion Motion in Quadrupole Fields

Ion motion in quadrupole fields is described in monographs (March & Hughes, 1989; Dawson, 1995). When written in terms of the variables

$$a_x = -a_y = \frac{8eU}{m\Omega^2 r_0^2}; \quad q_x = -q_y = \frac{4eV_{RF}}{m\Omega^2 r_0^2}; \quad \xi = \frac{\Omega t}{2} \qquad (2.15)$$

the equations of motion, 2.13, become

$$\frac{d^2x}{d\xi^2} + (a_x - 2q_x\cos 2\xi)x = 0$$

$$\frac{d^2y}{d\xi^2} + (a_y - 2q_y\cos 2\xi)y = 0 \qquad (2.16)$$

These are Mathieu equations. Solutions are classified as stable or unstable, which leads to the well-known stability diagram for a linear quadrupole shown in Figure 1. Ions oscillate with frequencies given by

$$\omega_n = (2n + \beta)\frac{\Omega}{2} \quad 0 \le \beta \le 1 \quad n = 0, \pm1, \pm2, \ldots \qquad (2.17)$$

where β is a function of a and q. The relation between β and q is given by Dawson (1995, p.70). For low values of q, and when $a = 0$, β is given by

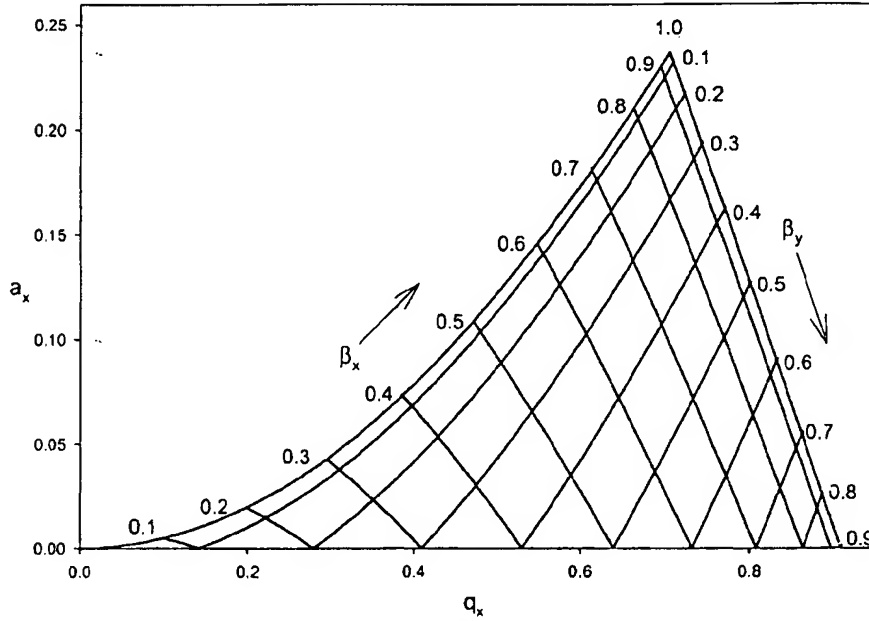$$\beta \approx \frac{q}{\sqrt{2}} \qquad (2.18a)$$

FIGURE 1. The first stability region of the linear quadrupole.

For values of q near the stability boundary at $q = 0.908$ where $\beta = 1$, q and β are related by (Sudakov, 2001)

$$q(\beta) = 0.908047 - 1.39869(1 - \beta)^2 \qquad (2.18b)$$

For low values of q, ion motion at the frequency with $n = 0$ in Equation 2.17 has the largest amplitude, and the motion is approximately harmonic with frequency

$$\omega_0 \approx \frac{q\Omega}{2\sqrt{2}} \qquad (2.19)$$

Within this approximation, ions behave as if they are confined in an effective electric potential, $V_{\text{eff}}(r)$, given by

$$V_{\text{eff}}(r) = D_{x,y}\left(\frac{r}{r_0}\right)^2 \qquad (2.20)$$

where the well depth in the x and y directions is given by

$$D_{x,y} = \frac{qV_{\text{RF}}}{4} \qquad (2.21)$$

For higher values of q, the contributions of the other frequencies in Equation 2.17 become increasingly important and the effective potential approximation is less useful.

4. Ion Motion in Higher Multipole Fields

In any inhomogeneous oscillating electric field, ions will move to regions of lower electric field. Thus linear ion traps

can be constructed not just with rod like electrodes, but with rings of alternating RF potential (Gerlich, 1992). However, most work in mass spectrometry uses multipoles constructed from rod arrays. Ion motion in pure quadrupole fields is complex, but at least the x and y motions can be considered separately, to give a stability diagram. For the higher multipoles, x and y motion are strongly coupled. The frequencies of ion oscillation and the stability of trajectories depend strongly on the initial conditions. For this reason, there is no stability diagram for motion in higher multipoles. Although a stability diagram can be calculated for a given set of initial conditions, the boundaries are diffuse (Haag & Szabo, 1986a,b; Gerlich, 1992). As a consequence, there is no sharp cutoff in transmission versus mass for ions that are at the edge of a stability boundary. For low values of the trapping voltages, ion trajectories in an RF multipole are determined approximately by an effective mechanical potential, U_{eff} (r), given by (Gerlich, 1992)

$$U_{\text{eff}}(r) = \frac{N^2}{4}\frac{(ze)^2}{m\Omega^2}\frac{V^2}{r_0^2}\left(\frac{r}{r_0}\right)^{2N-2} \qquad (2.22)$$

where N is the order of the multipole. The mechanical and electric effective potentials are related by

$$U_{\text{eff}}(r) = zeV_{\text{eff}}(r) \qquad (2.23)$$

Thus ion motion in a linear hexapole has an effective potential proportional to r^4, in an octopole proportional to

r^6 and so on. One consequence is that the ion motion is not harmonic, even within this approximation. The frequency of ion motion depends on the amplitude of motion. Another consequence is that the higher multipoles have relatively flat effective potentials near the central axis, and effective potentials that increase more rapidly near the rods. The shapes of the effective electric potentials for quadrupole, hexapole, and octopole fields are compared in Figure 2.

5. Linear Ion Guides, Collision Cells, and Traps

A linear RF multipole can be used to transport ions from a source to an analyzer. We refer to the device operated in this way as an "ion guide." If ions are deliberately injected into the multipole with sufficient energy that collisions with gas lead to fragmentation, we refer to the device as a "collision cell." A linear multipole is easily converted into a linear ion trap by applying stopping potentials to electrodes at the entrance and exit. Ions are then confined radially by the RF fields, and axially by the stopping potentials. We refer to the device operated in this mode as a linear ion trap. In contrast to the 3D ion trap, ions are not confined axially by RF potentials.

Unfortunately the term "linear" has two different common usages in the ion trap literature. Here we refer to a "linear trap" as a trap with an essentially 2D field as distinct from 3D Paul traps. However, in the 3D Paul trap literature, "linear" is sometimes used to refer to the case of a pure quadrupole field where the electric field is linearly proportional to the distance from the center and "nonlinear trap" to the case where there are field distortions described

by the addition of higher order multipoles, so that the linear relationship between distance and field no longer applies (Franzen et al., 1995). The situation becomes complicated because a trap or ion guide with a 2D field can also have higher order multipole fields, so that the electric field does not increase proportional to the distance from the axis. In this case, there is a linear device with nonlinear fields (e.g., Dawson & Whetton, 1969; Dawson, 1980). Finally, the central axis of a linear trap, formed from rods, can be curved (Drees & Paul, 1964; Church, 1969; Deutch et al., 1988; Waki et al., 1992; Bier, Park, & Syka, 1995; Lammert et al., 2000). We still refer to these traps as "linear" traps because the field between the electrodes is described essentially by 2D multipoles. The curvature of the central axis introduces field distortions.

6. Collisional Cooling

It was found in 1989 that the transmission of ions passing through a linear quadrupole ion guide and small aperture at the exit of the ion guide, increased as the gas pressure in the ion guide was increased (Douglas & French, 1992). While initially puzzling, this was soon explained as a collisional cooling effect. Provided ions in the quadrupole are not near a stability boundary, collisions of ions with a light bath gas cause the ions to lose kinetic energy and move toward the center of the quadrupole where the effective potential is lower. Thus transmission through a narrow exit aperture is increased. An example of the trajectory of an ion passing through a linear quadrupole with collisions is shown in Figure 3. The effect of collisions was modeled as a
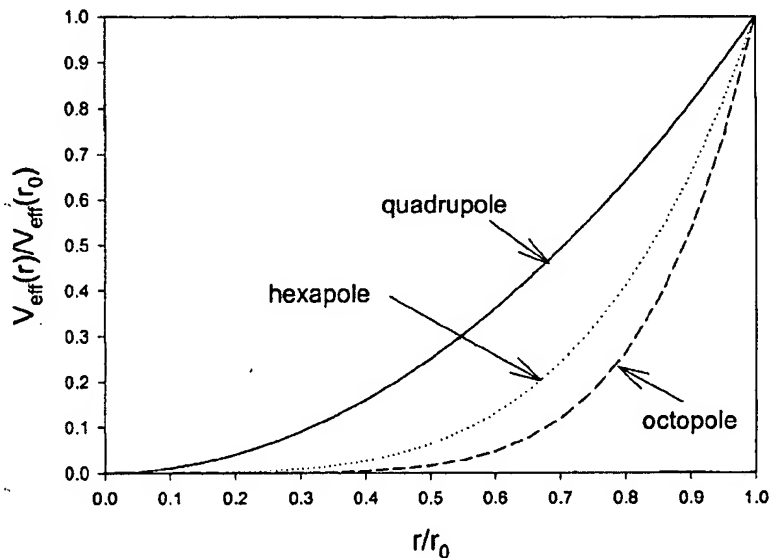

FIGURE 2. Comparison of effective potentials for quadrupole, hexapole, and octopole fields.
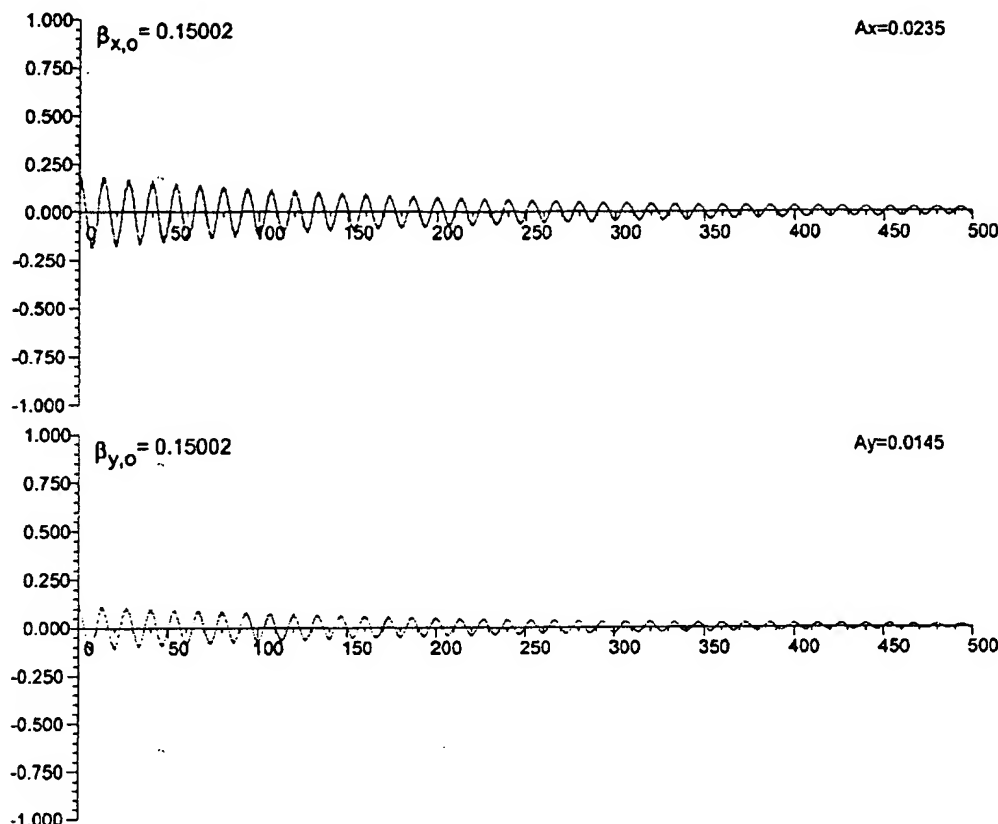
FIGURE 3. Ion trajectory through a linear quadrupole with collisions. The conditions were: ion $m/z = 612$, $q = 0.210$, collision gas N_2 at 3×10^{-3} Torr, collision cross section 250 Å^2, initial x displacement $0.2r_0$, initial y displacement $0.1r_0$, RF frequency 768 kHz, $r_0 = 4.0$ mm. The initial x and y velocities are zero. The vertical axis shows x and y displacement in units of r_0. The horizontal axis is time in number of RF cycles. Both the x and y motion are damped as the ion passes through the quadrupole.

continuous drag force using Equation 2.24 below. The damping of the ion oscillations is evident. Ions undergoing collisions also lose energy in the axial direction (Douglas & French, 1992). The effect is somewhat analogous to collisional cooling of ions in a 3D Paul trap (Neushauser et al., 1978; Stafford et al., 1984; March & Hughes, 1989, p. 17). Similar behavior is expected for ions passing through a higher order RF multipole. Because higher order multipoles have "flatter" pseudopotentials near the center than a quadrupole (Fig. 2), ions in higher multipoles are not confined so closely to the centerline.

Figure 3 shows only a single pass through an RF quadrupole ion guide. If ions are trapped in a multipole, they will travel repeatedly through the multipole and continue to lose energy. The final kinetic energy will be determined by a competition between collisional cooling of ions, which tends to produce a thermal distribution at the gas temperature, and heating of ions from the field of the trapping RF.

7. Ion Excitation in the Presence of a Collision Gas

Motion of ions trapped in a quadrupole field at the frequencies of Equation 2.17 can be excited with either dipole excitation or quadrupole excitation. Resonant excitation of ion motion was the subject of some of the first work with linear quadrupoles (Paul, Reinhard, & von Zahn, 1958). With dipole excitation, a small auxiliary voltage at a frequency of the ion motion is applied between a pair of opposite rods. With quadrupole excitation, the auxiliary voltage is applied in the same fashion as the main trapping quadrupole field. In both cases, excitation causes the amplitude of ion oscillation to increase and can lead to ion ejection or fragmentation.

If a buffer gas is present, the amplitude of motion increases initially, but then reaches a steady state. Collisions transfer kinetic energy to internal energy of an ion and this can lead to ion fragmentation. Even without fragmentation, collisions can damp the ion motion. The

effect of collisions is often modeled as a drag force proportional to the ion velocity (e.g., March & Hughes, 1989, p. 131). This model is most suitable when the ion speed is small relative to the thermal speed of the collision gas. When the ion speed is much greater than the thermal speed of the gas, the drag force is proportional to the square of the ion speed, because the number of collisions per second increases proportional to the speed, and the momentum transfer per collision also increases proportional to the speed. A model which describes the drag force for all ratios of the ion velocity to the neutral thermal velocity is based on drag coefficients, where the force on an ion is given by

$$F_d = -C_d \frac{\sigma n_g m_0 v^2}{2} \qquad (2.24)$$

where F_d is the drag force, σ is the ion-neutral collision cross section, n_g is the gas number density, m_0 is the collision gas mass, v is the ion speed, and C_d is a dimensionless drag coefficient which depends on the ratio of the ion speed to the thermal speed of the gas (Chen,

Collings, & Douglas, 1997). At low ion speeds, C_d is proportional to $1/v$ so that the force is proportional to the ion speed. At high ion speeds, C_d approaches a limit of 2.0 so that the force is proportional to the square of the ion speed. The value of C_d depends on the scattering dynamics. Two limits have been considered—specular (or hard sphere) scattering and diffuse scattering. For collisions of large ions of biomolecules with rare gases at ion energies of many electron volts, Chen, Collings, & Douglas (1997) concluded that diffuse scattering gave the best description of the drag force.

With dipole excitation, the auxiliary voltage has a frequency given by Equation 2.17, usually with n = 0. An example of a trajectory of an ion trapped in a quadrupole field with dipole excitation is shown in Figure 4. The effects of collisions were modeled using Equation 2.24. Initially, the amplitude of oscillation increases linearly. Eventually, a steady state is reached where the amplitude remains constant. This is very similar to excitation of a damped harmonic oscillator (Landau & Lifshitz, 1960, p. 77). For Figure 4, the damping force of Equation 2.24 was used,
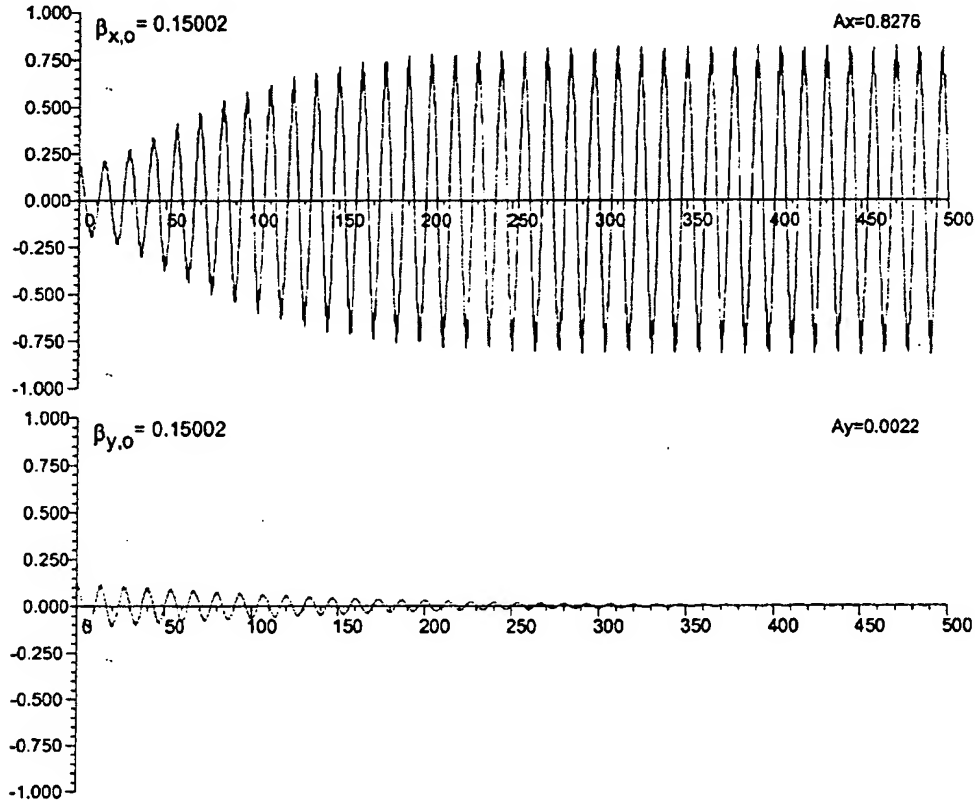

FIGURE 4. Ion trajectory in a linear quadrupole with dipole excitation. The conditions are the same as for Figure 3. Dipole excitation of 0.4 V is applied between the x rods. The amplitude of x motion increases linearly initially, but eventually a steady state is reached where the amplitude of oscillation remains constant.

with C_d for hard sphere scattering. Both the x and y motion can be excited together by applying dipole excitation simultaneously between the x rod pair and y rod pair (Raznikov et al., 2001). If the two excitation voltages differ in phase by $\pi/2$ (90°), circular motion of the excited ions is produced, and the average kinetic energy is twice that produced by simple dipole excitation.

With quadrupole excitation, the excitation waveform is applied to the electrodes in the same way as the trapping RF. Thus, the excitation circuit can be combined with the quadrupole power supply and no external transformers are needed (Cousins & Thomson, 2002). Collings & Douglas (2000) described a circuit for applying quadrupole excitation with an external oscillator and transformers. The description of quadrupole excitation, sometimes called parametric excitation (Landau & Lifshitz, 1960, pp. 80–83; Collings & Douglas, 2000; Sudakov et al., 2000), is considerably more complex than that of dipole excitation. For a harmonic oscillator, the parametric excitation frequencies, ω_{ex} are given by

$$\omega_{ex} = \frac{2\omega_0}{K} \qquad (2.25)$$

where ω_0 is the frequency of the unperturbed oscillator and K is an integer. For a harmonic oscillator with a damping force linearly proportional to the speed, there is a threshold value of the excitation force, f_{ex} given by

$$f_{ex} = \alpha\lambda^{1/K} \qquad (2.26)$$

where α is a constant and λ is the damping constant ($\sec^{-1}$) (Landau & Lifshitz, 1960, pp. 80–83). If the excitation force is above threshold, the amplitude of oscillation increases exponentially. If the amplitude is below threshold, the amplitude of motion decreases even when excitation is applied.

For ions trapped in a quadrupole field, the excitation frequencies (Sudakov et al., 2000) are

$$\omega_j^K = |j + \beta|\frac{\Omega}{K} \qquad j = 0, \pm 1, \pm 2, \ldots \qquad K = 1, 2, 3, \ldots$$

$$(2.27)$$

where K is the order of the excitation. For the $j = 0$, $K = 1$ resonance, the frequency of excitation is twice that of the fundamental frequency of oscillation ($n = 0$ in Eq. 2.17). For a given frequency of ion motion, determined by β, there are many excitation frequencies, determined by different j and K values. An example of the trajectory of an ion undergoing quadrupole excitation at the $j = 0$, $K = 1$ resonance is shown in Figure 5. The effects of collisions were modeled using Equation 2.24. Observation of the $j = 0$, $K = 1-6$ quadrupole resonances in a linear quadrupole ion trap coupled to a TOF mass analyzer have been reported (Collings & Douglas, 2000). Ions were excited

and depletion of the ions by ejection and dissociation was observed. The variation of threshold excitation voltage with K was found to follow Equation 2.26 closely. Observations of the resonances with $j > 0$ and $K \geq 1$ in a linear quadrupole trap coupled to a 3D trap have been described (Cha, 2002). For a given trap pressure, resonances with different j unexpectedly showed large differences in λ (Eq. 2.26).

8. Ion Isolation

For a least two reasons, it is useful to eject ions from a linear trap or to isolate ions of a selected mass to charge ratio. Excess unwanted ions can lead to space charge problems in the linear trap or in a downstream mass analyzer such as a Fourier transform ion cyclotron resonance (FTICR) or 3D trap. Ion isolation is necessary as the first step in MS/MS experiments in the trap. As with 3D Paul traps, ions can be isolated in a linear quadrupole ion trap by resonant excitation methods or by methods that use the boundaries of the stability diagram.

Either dipole or quadrupole excitation can be used to eject an ion of a selected mass to charge ratio from a quadrupole trap. To eject a range of m/z ratios, a fixed dipole or quadrupole auxiliary excitation voltage (at a frequency corresponding to ion resonance at a given q value, Eq. 2.19) can be applied. The main trapping RF voltage can then be changed to bring ions of different m/z ratios into resonance for ejection (Douglas, 1993). Alternatively, the excitation frequency can be scanned at a fixed trapping RF voltage.

A range of m/z ratios can also be ejected by applying multiple frequencies, either as a frequency scan or chirp, or as a broadband waveform, with a notch in frequency space. In a frequency scan, a range of frequencies is applied sequentially to the ion trap; ions that have frequencies of motion matching the applied frequencies are ejected. In a broadband waveform, all frequencies are present except for the frequency of an ion which is to be isolated. The first description of the use of broadband waveforms to eject ions from a linear quadrupole appears to be by Langmuir (1967). The broadband waveform can be generated by stored waveform inverse Fourier transform (SWIFT) methods (see, e.g., Marshall, Wang, & Ricca, 1985; Korner et al., 1996). Alternatively, a waveform containing sine or cosine waves at discrete equally spaced frequencies (typically 500 Hz) can be generated. Frequencies close to the resonant frequency of an ion to be isolated are omitted. All ions, except the selected ion, are ejected from the trap (Guan & Marshall, 1993; Julian & Cooks, 1993; Mordehai & Henion, 1993; Goeringer et al., 1994; Wells & Huston, 1995; Doroshenko & Cotter, 1996; Campbell, Collings, & Douglas, 1998; Cha, Blades, & Douglas, 2000; Collings et al., 2001). A broadband excitation waveform typically
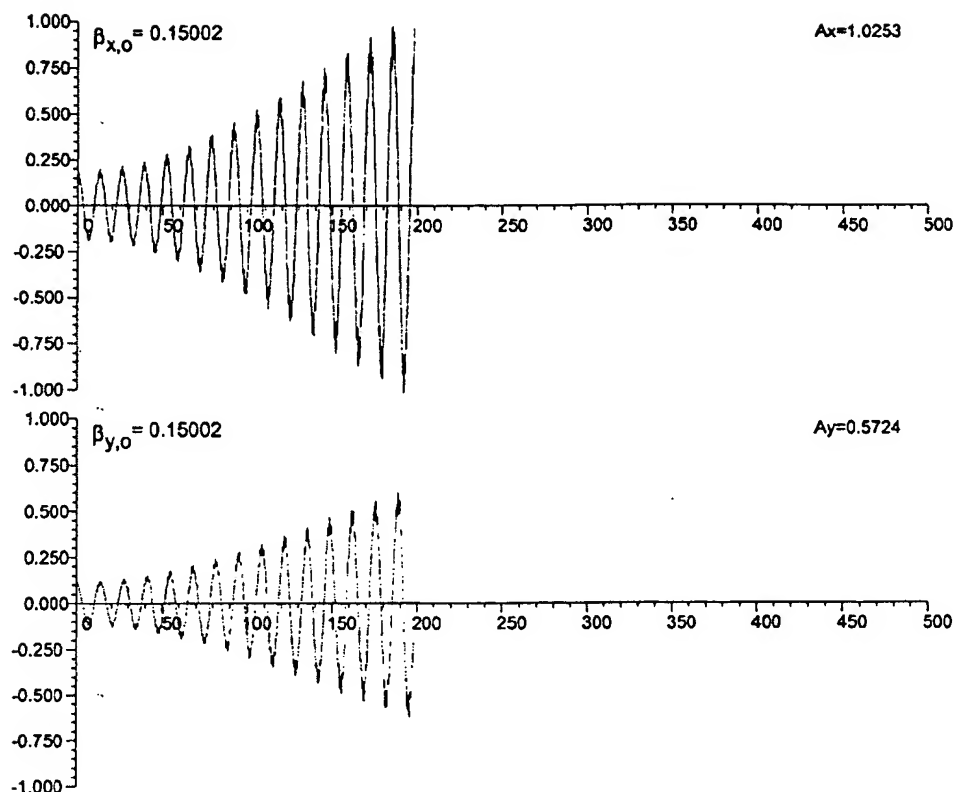
FIGURE 5. Ion trajectory in a linear quadrupole with quadrupole excitation. The conditions are the same as in Figure 3. Quadrupole excitation is applied and excites both the x and y motion. The amplitudes of oscillation increase exponentially and in this case the ion strikes the x rod after approximately 200 RF cycles.

requires less time to eject ions than a frequency sweep. Therefore, the duty cycle can be increased. As described by Louris & Taylor (1994), first generation broadband isolation waveforms for 3D traps required all trapped ions to experience the complete isolation event for complete removal of concomitant ions. A more recent technique produces uniform spectral coverage for the broadband isolation waveform regardless of the time ions enter the ion trap (Louris & Taylor, 1994). Therefore, ions can be isolated while the 3D trap is being filled. This method could equally be applied to linear quadrupole traps.

Boundary ejection methods take advantage of unstable ion motion at the boundaries of the stability diagram of a linear quadrupole (Fig. 1). An ion to be isolated is place near a stability boundary. Ions of neighboring mass to charge ratios have unstable motion and are ejected (Louris et al., 1990). An ion with a given m/z ratio can be isolated by placing it near the tip of the region at $a = 0.237$, $q = 0.706$ (Dawson, 1995, p. 21). If only a range of m/z ratios below a certain cutoff value needs to be ejected, the stability boundary at $a = 0$, $q = 0.908$ can be used. Dodonov et al.

(1997) showed that confining ions just inside the $a = 0$, $q = 0.908$ boundary can be used to cause excitation and fragmentation of ions. This was demonstrated for ions of bradykinin and endorphin. A disadvantage is that fragment ions with m/z values less than the precursor have $q > 0.908$ and are lost. Douglas (1993) proposed that the RF and DC voltages can be chosen to transmit a broad m/z range, whereas high and low mass ions are removed; this has been demonstrated by Harkewicz et al. (2002) with a quadrupole coupled to a Fourier transform mass spectrometers (FTMS) system. Recently this technique has found application in inductively coupled plasma mass spectrometer systems (Tanner, Baranov, & Bandura, 2002).

As discussed, there are no well-defined stability diagrams for higher order multipoles, and for this reason they have not been used as mass analyzers. However, the transmission still has some mass dependence. Voyksner & Lee (1999) were able to use this mass dependence with an octopole ion trap to reduce the levels of unwanted low mass ions in a linear-trap 3D-trap system. By applying DC as well as RF voltages between the rods of an octopole trap,

Wang et al. (2000) were able to achieve a mass resolution of 10. Although low, this resolution is useful for removing unwanted ions.

9. Trap Capacity

One of the attractive features of linear traps is that a greater number of ions can be stored than in a 3D trap. The volume of the trap can be increased simply by making it longer. One method to estimate the maximum ion density that can be stored in the trap is to assume there is a cylindrical cloud of ions with radius r_0, and that the electric field from the space charge of the ions is just balanced by the "electric field" from the pseudopotential. The magnitude of the electric field from the ions can be calculated from Gauss' law (Kip, 1969, p. 30) and (in SI units) is given by

$$|\vec{E}| = \frac{n_i e r_0}{2\varepsilon_0} \qquad (2.28)$$

where n_i is the ion number density. (Eq. 2.28 assumes the ions are singly charged.)

The magnitude of the equivalent electric field from the pseudopotential is

$$|\vec{E}| = \left| -\frac{\partial V_{\text{eff}}(r)}{\partial r} \right| . \qquad (2.29)$$

which, when $r = r_0$ gives

$$|\vec{E}| = \frac{q V_{\text{RF}}}{2r_0} \qquad (2.30)$$

Equating 2.28 and 2.30 gives the maximum ion density that can be stored in the trap as

$$n_{i,\text{max}} = \frac{q V_{\text{RF}} \varepsilon_0}{e r_0^2} \qquad (2.31)$$

or by comparison to Equation 2.21

$$n_{i,\text{max}} = \frac{4 D_{x,y} \varepsilon_0}{e r_0^2} \qquad (2.32)$$

A similar expression for the maximum number of ions that can be stored in a 3D trap can be derived (March & Hughes, 1989, p. 192)

$$n_{i,\text{max}} = \frac{3 D_z \varepsilon_0}{e z_0^2} \qquad (2.33)$$

where D_z is the effective potential well depth in the z direction, and z_0 is the distance from the center of the trap to an end cap. Comparison of Equations 2.32 and 2.33 shows that similar ion densities can be stored in linear and 3D quadrupole traps. It is the greater volume of linear traps that allows storage of more ions.

Based on these considerations, Campbell, Collings, & Douglas (1998) proposed that the ratio of the number of ions that could be stored in a 2D quadrupole trap, N_{2D}, to the number of ions that could be stored in a 3D trap, N_{3D}, is given by

$$\frac{N_{\text{2D}}}{N_{\text{3D}}} = \frac{r_0^2 l}{z_0^3} \qquad (2.34)$$

where l is the trap length. Equation 2.34 is essentially the ratio of the trap volumes.

Equation 2.31 gives the ion density for which trapping is no longer possible. Space charge effects appear at much lower densities. For example, Hager (2002a) found shifts and peak broadening of axially ejected ions, trapped at $\beta = 0.5$ ($q \approx 0.7$, $r_0 = 4.17 \times 10^{-3}$ m, $f = 1.00$ MHz), at an ion density of approximately 500 mm^{-3}. Equation 2.31 predicts that the maximum number of ions that can be trapped under these conditions is $n_{i,\text{max}} = 8.5 \times 10^5$ mm^{-3}. Thus Equation 2.31 is of little use in predicting the ion density at which ion frequencies shift and trap performance begins to degrade.

Equation 2.31 is based on the pseudopotential approximation and assumes ions completely fill the trap. Collisional cooling tends to shrink the ion cloud and estimates based on the cloud dimensions might be expected to be more realistic. Prestage, Dick, & Malecki (1989) gave an expression for the relative trap capacities as

$$\frac{N_{\text{2D}}}{N_{\text{3D}}} = \frac{3}{5} \frac{l_c}{R_{\text{sph}}} \qquad (2.35)$$

where l_c is the length of the cylindrical ion cloud in a 2D trap and R_{sph} is the radius of the spherical ion cloud in a 3D trap. Schwartz, Senko, & Syka (2002b) gave the ratio of the trapping capacities as

$$\frac{N_{\text{2D}}}{N_{\text{3D}}} = \frac{1}{2} \frac{R_{\text{2D}}^2 l_c}{R_{\text{3D}}^3} \qquad (2.36)$$

where R_{2D} and R_{3D} are the radii of the clouds in the 2D and 3D traps, respectively.

B. Mass Discrimination Effects

Several groups have identified and characterized potential mass discrimination problems associated with storing ions in linear traps. The effects can be classified as either shifts in the charge state envelope because of charge stripping, or depletion of ions because of ejection or fragmentation. Generally these problems arise when the trap is overfilled with ions so that space charge effects become serious, or when operating conditions are not set properly. In many cases, these experiments have been done with linear ion

traps combined with FTICR mass spectrometers (also referred to here as FTMS).

In some cases, charge transfer to background gas has been responsible for mass discrimination effects. For bovine ubiquitin ions, Senko et al. (1997) observed a charge state envelope of 7^+-13^+, with 11^+ the most intense, when the ions were accumulated in an FTMS cell. When ions were accumulated in a linear octopole trap (10^{-2} Torr) and then injected into the FTMS, they showed a charge state envelope of 7^+-12^+ with 9^+ being most intense. These shifts in charge state distribution were attributed to charge stripping or charge transfer to the background gas in the linear trap, which contained traces of solvents from the source; methods to limit solvent migration into the linear trap (lower ESI flow rates, higher inlet capillary temperatures, smaller diameter capillary or skimmer) reduced mass discrimination caused by charge stripping (Senko et al., 1997). Wood and co-workers provided a similar explanation in their study of ions of 2,000 Da poly(ethylene glycol) (PEG) accumulated in a linear hexapole ion trap (2×10^{-3} mbar), and then injected into an FTMS (Maziarz et al., 1999). Ion accumulation in the linear trap for 1 sec showed both singly and doubly charged ions, whereas ions accumulated for 5 sec showed only singly charged ions. Empirical optimization of the electrostatic potentials on the inlet ion optics was found to reduce mass discrimination. Mass discrimination was attributed to a combination of charge transfer in the trap and discrimination during injection of ions into the FTMS. With a 20 msec injection time and a cooling time of 2 sec for multiply charged horse myoglobin ions $(M + nH^+)^{n+}$, $n = 14-21$, in a linear quadrupole trap (5×10^{-5} Torr), Belov et al. (2001c) observed the most abundant charge state was 19^+. A cooling time of 20 sec produced lower charge state ions with 16^+ being the most intense. This again was attributed to charge transfer to the background gas.

In other cases, mass discrimination has been attributed to space charge effects. For a constant trapping time (100 msec) at a pressure of 5×10^{-5} Torr, an injection time of 20 msec, linear quadrupole trap entrance and exit lens potentials of 17 and 30 V, respectively, and a trap rod offset of 4 V, Belov et al. (2001c) observed, a broad charge state distribution ($\sim 11^+ - \sim 20^+$) for horse myoglobin ions, with $(M + 16H^+)^{16+}$ being the most intense. When the injection time was increased from 20 to 200 msec (higher space charge), the intensity of $(M + 20H^+)^{20+}$ increased significantly and the intensity for lower charge states decreased. Belov et al. (2001b) suggested that m/z dependent radial stratification occurs in the linear trap with higher m/z ions at the outer edge and lower m/z ions closer to the center of the trap. It was argued that "concentric shells" of ions of different m/z ratios are formed in a linear quadrupole trap (Tolmachev, Udseth, & Smith, 2000; Belov et al., 2001b).

This conclusion was based on the observation that ejection of higher m/z ions with dipolar excitation required lower excitation amplitudes in comparison to lower m/z ions (Belov et al., 2001b). Increasing space charge causes ions with higher m/z to increase their radial distance, which may promote ion ejection (Belov et al., 2001c). An alternative explanation is that for a given trapping voltage the effective potential well depth decreases as m/z increases (because q decreases) (Eq. 2.21).

When the linear trap entrance and exit lens potentials were changed from 17 and 30 V to 18 and 21.5 V, respectively, Belov et al. (2001c) observed, for horse myoglobin ions, a broad charge state distribution $\sim 13^+ - \sim 19^+$ with $(M + 16H^+)^{16+}$ being most intense when the ions were injected for 20 msec and trapped for 100 msec. When the injection time was increased to 200 msec, the intensity of all charge states except $(M + 16H^+)^{16+}$ decreased (Belov et al., 2001c). Depletion of the higher m/z ions was again rationalized using the radial stratification theory, but discrimination against high m/z was also attributed to the fringing fields at the entrance and exit of the trap. It was proposed that ions in the fringing fields could be lost through ejection (Belov et al., 2001c) or fragmentation (Belov et al., 2001d). As might be expected, significant mass discrimination was also observed if the axial stopping potentials were comparable to the analyte ions' translational energies (Belov et al., 2001c). Again this was attributed to ion "interactions" with the fringing fields. To reduce discrimination problems, the stopping potential should significantly exceed the analyte ions' translational energies (Belov et al., 2001c; Collings et al., 2001). However Belov et al. (2001c) argued that if the exit and entrance stopping potentials are excessively high, while ions will no longer be subjected to fringing fields, the charge density along the trap axis will increase, and Coulombic repulsion will cause ions to redistribute radially (Belov et al., 2001d).

Space charge distorts the first stability region for linear quadrupole ion traps. Belov et al. suggested that for an RF only linear quadrupole trap at maximum space charge capacity, the Mathieu stability parameter, q, corresponding to the low m/z cutoff is ~ 0.68 rather than 0.907 (Belov et al., 2001c). Therefore, a greater range of low m/z ions are unstable with space charge (Belov et al., 2001e). Ions with higher m/z ratios (low charge states) can be ejected or dissociated because of high amplitudes of motion caused by radial stratification or fringing fields; low m/z ions can be ejected because of an increase in the low mass cutoff (Belov et al., 2001c). This gives discrimination against both high and low m/z ions.

Hofstadler and co-workers (Sannes-Lowery et al., 1998) first observed ion dissociation that they termed "multipole storage assisted dissociation" (MSAD) in a hexapole linear ion trap. This has been investigated by

several groups (Håkansson et al., 2000; Sannes-Lowery & Hofstadler, 2000; Belov et al., 2001d,e; McDonnell et al., 2002). Fragmentation of bovine ubiquitin ions was observed to depend on the number of ions accumulated in the linear trap and the potential well formed by the trap entrance and exit lenses (Sannes-Lowery et al., 1998). Belov et al. (2001d) observed similar effects with peptide ions in a linear quadrupole trap. Sannes-Lowery et al. (1998) found that with a 0.6 μM solution of ubiquitin infused at 1.5 μL min^{-1}, ions could be stored for ≥2.5 sec before the onset of fragmentation, whereas with a 10 μM solution, fragmentation was observed in 1.15 sec. For ubiquitin ions, low energy dissociation channels were favored and produced mostly y type ions (Sannes-Lowery et al., 1998). Work by Håkansson et al. (2000) also showed low energy collisionally activated dissociation. Sannes-Lowery & Hofstadler (2000) used a solenoid-activated shutter to gate ions into their hexapole linear trap to characterize ion dissociation as a function of storage time and ion number. No significant ion fragmentation was observed for a 20-mer phosphorothioate oligonucleotide using low space charge conditions (500 msec ion accumulation) regardless of the trapping time (0–4.5 sec). However, extensive fragmentation was observed as the ion accumulation time increased, regardless of the trapping time. For high space charge conditions (2 sec ion accumulation) in a low pressure (5.4 × 10^{-6} mbar) linear ion trap and with "gentle" orifice/skimmer conditions, no fragmentation was observed for a 20-mer phosphorothioate oligonucleotide; increasing the pressure in the linear trap to 3.5 × 10^{-5} mbar produced significant fragmentation. Regardless of the linear trap pressure, "gentle" orifice/skimmer conditions and low space charge conditions produced "no significant fragmentation" (Sannes-Lowery & Hofstadler, 2000).

A series of studies by Smith's group described similar observations of dissociation in a linear quadrupole trap. Belov et al. (2001c) reported that increasing the number of charges in a low pressure linear trap (~10^{-5}Torr) led to ion fragmentation and a decrease in analyte ion signal intensity. When singly and doubly charged ions (bradykinin, gramicidin S, and angiotensin I) were accumulated for 300 msec, singly charged ions were ejected. Doubly charged ions exhibited significant dissociation attributed to RF heating (Belov et al., 2001c).

Many of these problems can be eliminated. Keeping the charge density low in a linear trap, by using short ion injection times and by using ion isolation techniques (*vide supra*), will greatly reduce or eliminate many of the mass discrimination effects caused by space charge. Ion interactions with fringing fields, which typically penetrate ~$2r_0$ into the quadrupole (Hunter & McIntosh, 1989; McIntosh & Hunter, 1989), can be minimized by using a sufficiently high bias between the trap DC offset and the gating

electrodes or by using a set of short RF-only rods for the entrance and exit gates (Schwartz, Senko, & Syka, 2002a,b). Increasing the pressure in the linear trap (10^{-3} Torr) also appears to minimize mass discrimination, probably because collisional cooling of ions prevents large amplitudes of radial motion which can cause ion ejection or fragmentation (Belov et al., 2001e).

Belov et al. (2001f) noted that a low amplitude dipole excitation also helps to minimize mass discrimination effects. Horse myoglobin ions accumulated in a linear quadrupole trap for 1,000 msec showed significant mass discrimination; the $(M + 15H^+)^{15+}$ ion intensity was significantly greater than that of any other charge state. Dipolar excitation using a low amplitude (50 mV$_{p-p}$) auxiliary RF at the secular frequency of the $(M + 15H)^{15+}$ ion reduced the charge state discrimination (Belov et al., 2001f). A 277 msec auxiliary RF pulse produced a narrow charge state distribution $(14^+ – 16^+)$, whereas a longer auxiliary RF pulse (694 msec) produced a broad charge state distribution $(11^+ – 20^+)$. It was concluded that the auxiliary excitation reduced the charge density (space charge) along the axis of the trap thereby reducing the charge state discrimination (Belov et al., 2001f). The effect may be similar to that in 3D Paul traps where dipole excitation in the presence of space charge introduces coherent motion of the center of mass of the entire ion cloud, to produce a more uniform charge distribution in the trap (Sevugarajan & Menon, 2000). A broadband excitation waveform (e.g., SWIFT) causes similar behavior, and would be useful when the mass spectrum is not known *a priori* (Belov et al., 2001f).

III. LINEAR TRAPS COMBINED WITH OTHER MASS ANALYZERS

A. Linear Traps Combined with 3D Paul Traps

3D ion trap (or Paul trap) mass spectrometers are widely used but have limitations. With a continuous source, such as ESI, ions generated while the 3D trap is processing other ions are not used, thereby limiting the duty cycle. Furthermore, the total number of ions that can be stored in a 3D ion trap is limited by space charge effects. Combining a linear trap with a 3D trap can help overcome these limitations.

While Douglas (1993) was first to describe coupling a linear multipole trap to a 3D ion trap, Voyksner & Lee (1999) were the first to publish experimental results showing some of the advantages of this combined system. Voyksner & Lee (1999) used a commercial 3D ion trap mass spectrometer with an octopole ion guide as the linear trap. Their instrument had four stages of differential pumping and the base pressure of the linear and 3D trap chambers were 10^{-4} and 10^{-6} Torr, respectively. Cha, Blades, &

Douglas (2000) also described a combined linear quadrupole ion trap 3D trap system. A linear quadrupole ion guide, q0, was operated at a pressure of 7×10^{-3} Torr, whereas the linear and 3D traps operated at 7.5×10^{-4} Torr. This configuration allowed ion storage and cooling in q0 prior to admission of ions to the lower pressure linear trap, that is, when the linear trap entrance lens was gated closed.

To improve the duty cycle, ions are accumulated in the linear trap, whereas the 3D trap performs other functions such as CID or mass analysis. In the simplest case, the duty cycle of a 3D ion trap coupled directly to a continuous ion source is (Douglas, 1993)

$$\text{Duty cycle} = \frac{T_C}{T_C + T_{A,3D}} \qquad (3.1)$$

where T_C is the ion trap fill time, and $T_{A,3D}$ is the time for MS analysis in the 3D trap. Douglas (1993) provided a hypothetical example where the mass analysis time of a 3D trap is 100 msec, an ESI source produces 6.2×10^8 ions sec^{-1}, and 1×10^6 charges are trapped in the 3D trap. The trap fills in $\sim 1.6 \times 10^{-3}$ sec. The duty cycle is only $\sim 1.6\%$. More than 98% of the ions from the ion source are discarded.

The duty cycle improves significantly when a linear trap is used to pre-concentrate analyte ions and remove unwanted ions prior to MS analysis in the 3D trap (Douglas, 1993; Voyksner & Lee, 1999; Cha, Blades, & Douglas, 2000). In this case, the duty cycle calculation is more complicated and depends on the details of the experiment. Assume that the ion current and the 3D ion trap charge capacity are the same as in the previous example, that unwanted concomitant ions represent 90% of the total ion current, and that the remaining 10% of the total ion current is analyte ions. If analyte and concomitant ions are trapped in a linear trap and the concomitants are simultaneously removed by resonant ejection or other means, the time to fill the linear trap with analyte ions can be increased to ~ 16 msec (Douglas, 1993) a tenfold improvement. If ions are collected in a linear trap for a period T_L, processed in the linear trap for a time $T_{A,2D}$ emptied into a 3D trap for a time T_E and then processed in the 3D trap for a time $T_{A,3D}$, the duty cycle is

$$\text{Duty cycle} = \frac{T_L}{T_L + T_{A,2D} + T_E + T_{A,3D}} \qquad (3.2)$$

However, ions can also be accumulated in the linear trap while the 3D trap is processing ions, so that the duty cycle increases to

$$\text{Duty cycle} = \frac{T_L + T_{A,3D}}{T_L + T_{A,2D} + T_E + T_{A,3D}} \qquad (3.3)$$

In favorable cases, the duty cycle can be nearly 100%.

When trace analyte ions are to be detected in the presence of a large excess of concomitant ions, the trace ions can be isolated in the linear trap before injection into the 3D trap (Douglas, 1993; Voyksner & Lee, 1999; Cha, Blades, & Douglas, 2000). Because unwanted ions are removed, the linear dynamic range for trace analyte ions can be extended. Voyksner & Lee (1999) described the first experiments designed to select analyte ions in a combined linear trap 3D trap instrument. An RF octopole ion guide was used as a high-pass mass filter to remove low mass ions (Voyksner & Lee, 1999). The frequency and RF amplitude were optimized to improve either the sensitivity or low m/z cutoff mass resolution. The conditions for optimum sensitivity did not provide the highest mass resolution. A mixture of betaine, adenosine, lincomycin, and polyalanine was used to evaluate this technique. The betaine tetramer $(4\,M - H_2O + H^+)^{1+}$ was $ca.$ 1.3% of the total ion current. With no ion isolation, space charge effects in the 3D trap gave a mass assignment error of ~ 1 Th. When the octopole ion guide functioned as a trap and high-pass filter to remove low-mass concomitant ions, the concentration of the trace analyte ions in the 3D ion trap increased. Overall the sensitivity increased by $\sim 10\times$ and masses were correctly assigned. Voyksner & Lee (1999) also compared ion isolation in the linear and 3D traps. For the same number of ions, trapping in the linear trap and using high-pass filtering increased the sensitivity by $\sim 40\%$ when compared to direct ion injection into the 3D trap with simultaneous application of a FNF waveform to the 3D trap (Voyksner & Lee, 1999).

Cha, Blades, & Douglas (2000) investigated the mass resolution with resonant ejection of ions from a linear quadrupole trap. With ion ejection at the fundamental frequency ($n = 0$, Eq. 2.17), the frequency resolution, $f/\Delta f$, equals the mass resolution at low q. A maximum frequency resolution of approximately 250 (fwhm) for dipolar excitation of reserpine $(M + 1H^+)^{1+}$ ions at $q = 0.70$ was reported. The excitation was applied for 100 msec and the trap pressure was 7.5×10^{-4} Torr. The resolution decreased at lower q values and with shorter excitation times. Although moderate, this resolution is far higher than that obtained in hexapole or octopole traps, and allows isolation of an analyte ion from unwanted ions on both the low and high mass sides of the analyte ion.

Cha, Blades, & Douglas (2000) demonstrated isolation of trace reserpine ions in a large excess of poly(propylene glycol) (PPG) ions. When ions from a solution of poly(propylene glycol)/reserpine (500/1) were injected directly into their 3D trap, the trace reserpine ions could not be identified because of poor resolution, sensitivity, and mass accuracy caused by the space charge of the much more abundant PPG ions. However, isolation of reserpine ions in the linear trap prior to injecting the ions into the 3D trap increased the sensitivity of the 3D trap by a factor of

16; unit mass resolution was possible, and the mass accuracy also improved. With external ion isolation, a linear response to trace concentrations of reserpine (0.2–5.0 μM) in a large excess of PPG (350 μM) was shown. Ion isolation could also be performed in the 3D trap. However, they found for their system that the sensitivity was ~5× greater with ion isolation in the linear trap.

Recently, Hardman & Makarov (2003) have described the use of a linear quadrupole trap to store ions formed by ESI for injection into an orbitrap mass analyzer (Makarov, 2000). Ions passed through an orifice and skimmer, a quadrupole ion guide for ion cooling and then entered the quadrupole storage trap. The quadrupole trap had two rod sets; short rods near the exit were biased so that most ions accumulated in this region. Because the orbitrap requires that ions be injected in very short pulses, kilovolt ion extraction potentials were applied to the exit aperture. Flight times of ions to the orbitrap were mass dependent, but for a given mass, ions were injected in bunches less than 100 nsec wide (fwhm).

B. Linear Ion Traps Combined with TOF Mass Analyzers

A TOF mass spectrometer can also have a low-duty cycle when coupled with a continuous ion source. Combining an ion trap with a TOF mass analyzer can improve the duty cycle. Both 3D (Micheal, Chien, & Lubman, 1992, 1993; Chien, Micheal, & Lubman, 1994; Li & Purves, 1995; Purves & Li, 1997; Doroshenko & Cotter, 1998) and linear traps have been combined with TOF mass analyzers. A trap can also add MS^n capabilities to the system.

Using SIMION calculations, Ijames (1996) proposed coupling a TOFMS oriented orthogonally to a linear ion trap. Ions generated by ESI enter the ion trap through conventional RF ion guides. After accumulation, ions are confined axially in the trap by elevated DC offsets on end rod sets, collisionally cooled, then extracted radially, between a pair of rods. This radial ion extraction method was further discussed in a patent by Franzen (1998). Four or six parallel pole rods extend orthogonally across the flight path and ions can be ejected radially out of the trap and into the flight path. With a hexapole ion trap, a DC voltage is applied to a repeller plate and the voltages on the hexapole rods are switched to DC. Higher DC potentials are applied to the rods close to the repeller plate compared to potentials on rods close to an ion extraction aperture plate. An approximately uniform extraction electric field is formed. Ions pulsed out of the trap are focused by a cylindrical einzel lens and enter the TOFMS. Franzen noted that rapidly switching the pole rods from RF voltages to high DC voltages for ion extraction is not easy technically. An alternative arrangement using a linear ion trap was proposed. Four rods are arranged asymmetrically so that two rods close to an ion extraction aperture plate have wider spacing than two other rods close to a repeller plate. When the RF on the rods is switched off and the ion extraction aperture plate is at the voltage of the flight tube, ions are drawn out by the penetrating field and accelerated. The efficiency of ion confinement in this field was not discussed. No experimental data and no further development of this method are found in the literature.

A linear ion trap coupled either orthogonally or co-axially to a TOFMS, with axial ion release from the trap, was proposed by Dresch, Gulcicek, & Whitehouse (1997). The multipole trap (quadrupole, hexapole, or octopole) with a conical skimmer and an aperture plate to act as the entrance and exit gates, respectively, operates between an atmospheric pressure ion source and the acceleration region of a TOFMS. By adjusting the bias voltages on the skimmer, multipole, and exit lens, the system can operate with either ion storage or continuous transmission. The ion guide extends through two vacuum pumping stages, and the background gas, in viscous flow at the entrance section, changes to molecular flow in the lower pressure exit section. It was argued that with this nonuniform pressure distribution, ions reflected back from the exit section have more collisions in the entrance section and reach thermal equilibrium more "efficiently." At the same time, ions from the source can constantly fill the trap. By adjusting the width of the trap exit pulses and the delay between the exit pulses and the TOF source pulses, ions with a relatively narrow selected m/z range enter the TOF source. The intensity of selected tri-tyrosine ions ($m/z = 508$) in a mixture of valine ($m/z = 118$), tri-tyrosine and hexa-tyrosine ($m/z = 997$) could be increased by a factor of 39 with this method. However, other ions were lost. Because of the different voltage settings on the focusing lenses after the trap exit electrode in this mode, ions shift to lower flight times compared to flight times in the continuous mode. This can make mass calibration over a broad range difficult.

Multipole ion guides, TOF coupling methods, and MS^n were also discussed in later patents (Whitehouse, Dresch, & Andrien, 1998, 2000; Whitehouse, Andrien, & Gulcicek, 1999). Segmented multipole ion guides that passed through two stages of differential pumping were described. In other arrangements, separate ion guides were used in each pumping stage. With a quadrupole, ion isolation or selection can be achieved as described above; isolation near the tip of the stability region, resonant ejection of unwanted ions, and trapping ions with $a > 0$. Ion activation for fragmentation could be achieved by resonant excitation. It was proposed that ion activation could also be achieved by switching the offset of the ion guide and the voltage on the exit lenses to accelerate ions that are in the fringing field at the time of the voltage switch. A third fragmentation method involved filling the trap with ions until fragmentation occurred (no ion isolation step was included). This was

demonstrated with ions of leucine enkephalin (White-house, Dresch, & Andrien, 1998, 2000; Whitehouse, Andrien, & Gulcicek, 1999). The peptide ions dissociated when the fill time was increased from 0.5 to 1.65 sec. The mechanism for the dissociation was not explained although it may be related to multipole storage assisted dissociation, discussed above. Ion isolation and excitation by resonant excitation to give MS^n were discussed. Several multipole ion guides were proposed (Whitehouse, Dresch, & Andrien, 1998; Whitehouse, Andrien, & Gulcicek, 1999). Three independent quadrupole ion guides were configured with the same radial cross section geometries with adjacent poles axially aligned. Operation of the multiple ion guides becomes complex. Ion isolation or fragmentation can be achieved by combinations of different selection and fragmentation methods in any of the quadrupole assemblies. Ions leaving the ion guide in a timed fashion are selectively extracted into the flight tube. Ions not accelerated into the TOF were monitored by a detector outside the TOF source on the side opposite to the trap. Although many ideas on

combining linear traps and TOFMS are found in these patents, experimental data are limited.

Coupling a linear ion trap and TOFMS orthogonally has been described extensively by Douglas and co-workers. As shown in Figure 6 (Campbell, Collings, & Douglas, 1998; Douglas, Campbell, & Collings, 2000), ions formed by ESI pass through a curtain gas, a sampler and a skimmer and enter an RF-only quadrupole ion guide and a linear quadrupole ion trap at a pressure of 7 × 10^{-3} Torr. This system can be operated in three modes: (1) in a continuous flow mode, ions from the source are not trapped and simply pass through the two sets of quadrupole rods where they are collisionally cooled, and then enter the source region of the TOFMS; (2) in a trapping mode, ions are injected into the trap and confined, to improve the duty cycle of the system; (3) for MS^n, ions of interest can be isolated by a broadband waveform notched in frequency space, and subsequently fragmented with dipole excitation applied between a pair of the quadrupole rods. In all modes, ions are accelerated into the flight tube by high voltage
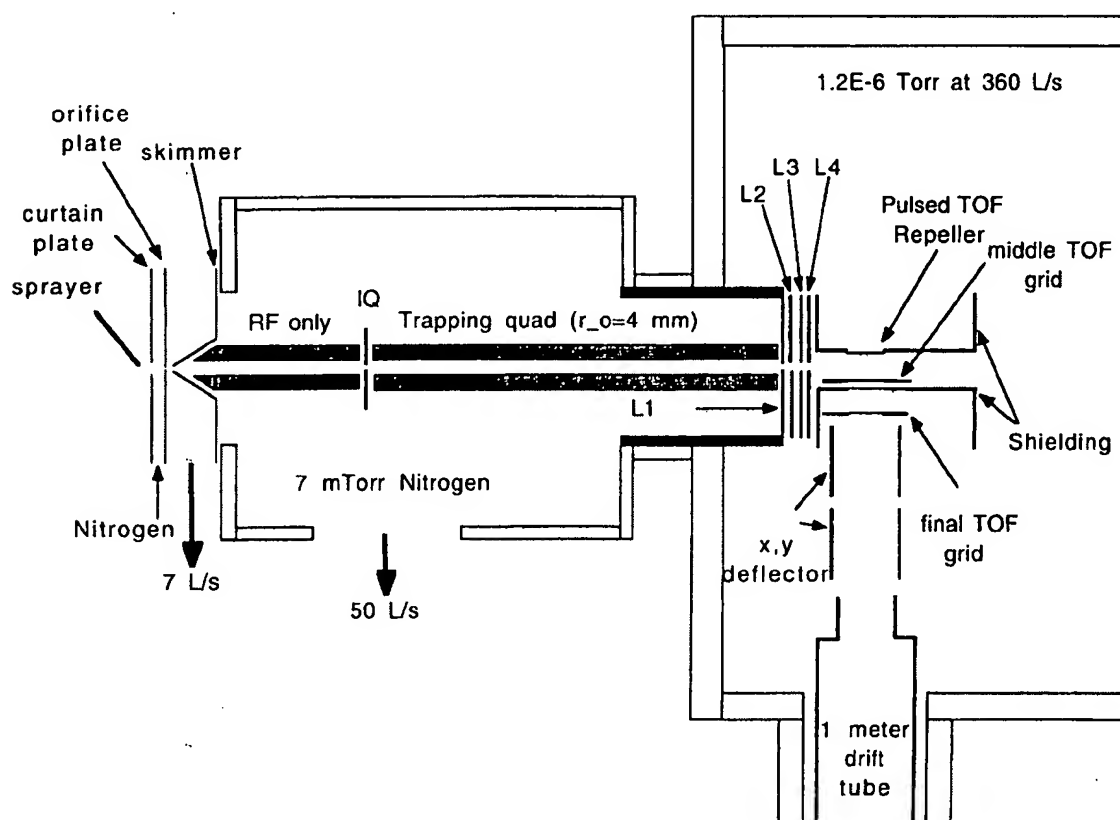

FIGURE 6. Schematic diagram of a linear quadrupole ion trap coupled orthogonally with a linear TOFMS. IQ, L1, L2, L3, and L4 are aperture plates. IQ and L1 served as the trap entrance and trap exit, respectively, whereas L2, L3, and L4 are focusing lenses. Reproduced with permission from Campbell, Collings, & Douglas (1998). Copyright 1998 John Wiley & Sons Limited.

pulses on the TOF repeller and the TOF extraction grid, and detected with microchannel plates (MCP). Because the velocity of the ions leaving the quadrupole can induce a drift angle off the flight direction in the TOF, sets of deflectors in the x and y directions can be employed to minimize ion loss in the flight tube. Figure 7 shows a demonstration of MS^3 of the +3 ion of renin substrate tetradecapeptide (Collings et al., 2001). Figure 7a shows a mass spectrum of the peptide prior to isolation of $m/z = 587$ precursor ions. These ions, shown in Figure 7b, were isolated by a notched broadband waveform (25 V_{0-p} pole-to-ground, 5 kHz notch centered at 217.5 kHz) applied for 4 msec. For fragmentation with dipolar excitation, an auxiliary AC voltage (amplitude 0.625 V_{0-p}, 217.5 kHz) was applied for 1 msec. The fragment spectrum is reproduced in Figure 7c. The first generation product ions at $m/z = 747$ were selected with a broadband waveform with a

FIGURE 7. MS^3 of the +3 ion of renin substrate tetradecapeptide. Excitation of the peptide was carried out at q ≈ 0.6 for $m/z = 587$ at a trapping pressure of 4 mTorr of nitrogen. Reproduced with permission from Collings et al. (2001). Copyright 2001 John Wiley & Sons Limited.

5 kHz notch centered at 164.5 kHz with amplitude 25 V_{0-p} (Fig. 7d), and subjected to fragmentation by an additional auxiliary AC voltage (0.625 V_{0-p}, 164.5 kHz) (Fig. 7e). These ion isolation/fragmentation steps can in principle be repeated provided that the fragments generated in each step have sufficient intensity.

Excitation of ions in a linear quadrupole ion trap involves a competition between radial ejection and fragmentation. Higher auxiliary voltages lead to ion ejection. With excitation at lower voltages, Campbell, Collings, & Douglas (1998) observed a threshold time for dissociation. Excitation times substantially greater than the threshold time gave no increases in fragment yield (Campbell, Collings, & Douglas, 1998). The background gas pressure also played an important role in ion excitation. At higher background gas pressures, higher excitation amplitudes were required for ion fragmentation and the excitation frequency resolution decreased. At lower trap pressures, because there was less collisional cooling, higher stopping voltages on the entrance and exit plates were required to confine ions (Collings et al., 2001).

The resolution possible with dipole or quadrupole excitation of ions at higher order excitation frequencies ($n > 0$ in Equation 2.17 with dipole excitation, $j = 0$, $K \geq 1$ in Eq. 2.27 with quadrupole excitation) was investigated with the linear-trap linear TOF system. It is necessary to distinguish the frequency and mass resolutions. As shown in Figure 8, the frequency resolution with dipolar excitation increased by a factor of 2.4 when reserpine ions ($m/z = 609$) were excited at the first overtone frequency ($n = 1$ in Eq. 2.17), whereas the mass resolution decreased by a factor of 3.1 (Collings et al., 2001). With quadrupole excitation (Collings & Douglas, 2000), it was found that the mass resolution for depletion of reserpine ions increased approximately linearly with K (Eq. 2.27) from approximately 120 at $K = 1$ to 232 at $K = 6$. The observed resonant frequencies were found to have small shifts from the theoretical values. The shifts depend on the excitation amplitude and background gas density. An ion trajectory simulation (Collings, Sudakov, & Londry, 2002) showed that the excitation amplitude is most responsible for the resonance shifts, and the shifts were explained in terms of a stability diagram based on the Mathieu equation.

The performance of this linear ion trap linear TOF mass spectrometer system has been explored. A cluster ion $Cs_{63}I_{62}^+$, $m/z = 16,240.5$, was detected to demonstrate the high m/z range possible (Collings et al., 2001). The mass resolution was increased from several hundred to ca. 5,000 at m/z 750 by replacing the linear TOF with a reflectron (Collings et al., 2001). In addition, this system was used to study the gas phase H/D exchange with D_2O and CD_3OD of ions of bradykinin (Mao & Douglas, 2003), myoglobin (Mao, Ding, & Douglas, 2002), and lysozyme (Mao et al., 2003). With bradykinin, the hydrogen exchange levels of
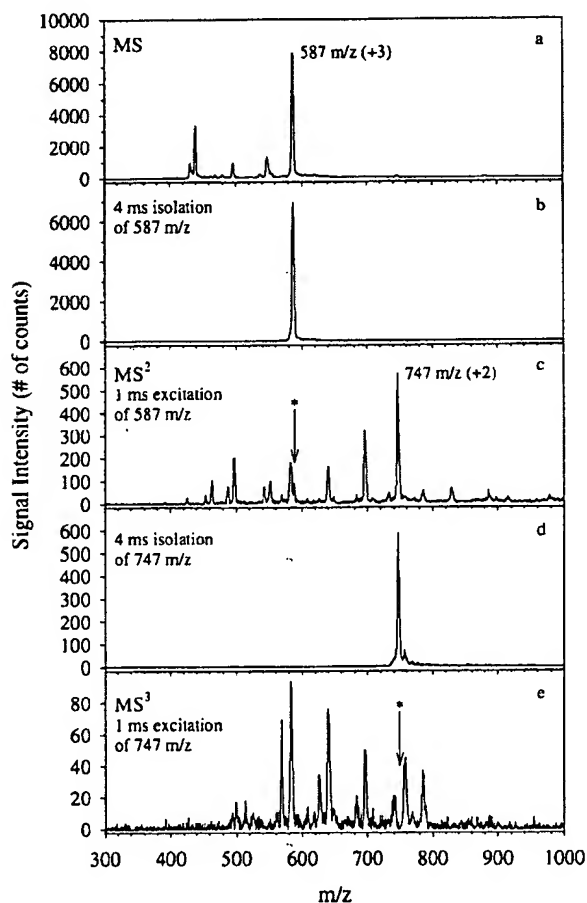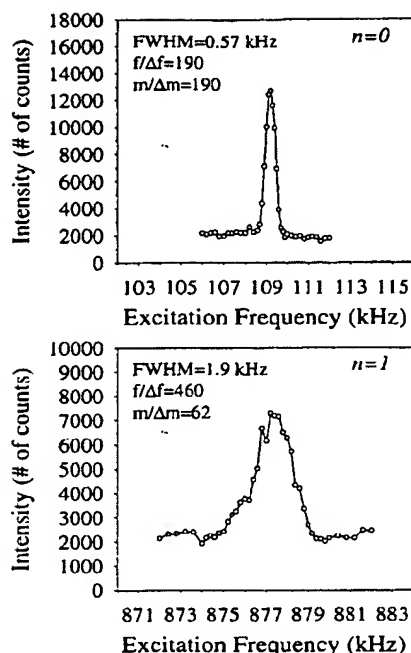
FIGURE 8. Dipole excitation of reserpine ($m/z = 609.7$) at $q \approx 0.39$. The signal is the integrated intensity of the fragment ions over the range $m/z = 181-601$. The excitation amplitude was 0.113 V_{0-p} and 1.56 V_{0-p} for the $n = 0$ and $n = 1$ resonances, respectively. Reproduced with permission from Collings et al. (2001). Copyright 2001 John Wiley & Sons Limited.

sodiated and singly and doubly protonated molecular ions were found to be comparable to those found in earlier FTMS experiments (Freitas & Marshall, 1999). Because the pressure of the deuterating agent in the linear trap can be ca. 10^{-3} Torr, the exchange required only seconds compared to minutes or even hours in FTMS experiments.

In the experiments of Douglas and co-workers, ions were simply allowed to drain from the trap into the TOF source (Campbell, Collings, & Douglas, 1998; Collings et al., 2001). Chernushevich and Thomson noted that with a QqTOF system (Chernushevich & Thomson, 1999, 2001, 2002, 2003; see also Chernushevich, 2000), the heaviest ions must reach the detector in the TOF before the next pulse of ions is accelerated into the flight tube, and this places a limit on the duty cycle. As well lighter ions leave the trap and enter the TOF source region with greater velocities than heavier ions. The optimum time to pulse the TOF depends on the m/z ratio of interest. To improve the sensitivity, for either precursor or fragment ions, when the collision cell was operated as an ion trap, a timed ion release method was used to select a relatively narrow m/z window. Experiments showed that the fragment ion signal could be increased significantly when ions were released

from the ion trap in pulses. A fragment ion at $m/z = 86$ from a precursor peptide ion, ALILTLVS ($m/z = 829$) was found to be seventeen times more intense with an optimized delay of 22 μsec between the ion release pulse on the trap and the source pulse of the TOFMS, compared to the signal without trapping and pulsing (Chernushevich, 2000). However, ions of higher m/z were not detected because of the mass selection with the delayed pulses. The delay between the two pulses greatly affected the ion intensity, and the observed mass envelope and the mass resolution were found to depend on the amplitude and the duration of the pulse on the trap exit aperture. The results are generally applicable to other linear trap-TOF systems.

Chernushevich & Thomson (2003) found that the mass range of enhanced intensity depends on the distance between the trap exit and the acceleration region of the TOF (Chernushevich & Thomson, 2003). On their instrument, signal increases that reached a maximum at a given m/z fell gradually, and at $(m/z)/2$ and $(3m/z)/2$ there were no enhancements. This observation led to an algorithm to increase the ion intensities over a wide range in product ion scans on a QqTOF. The entire mass range is divided into several intervals. The spectrum for each interval is acquired in a fraction of the total acquisition time. Because the ion transmission in the collision cell is mass dependent, the RF voltage on the collision cell quadrupole rods is increased for each interval of increasing mass. The duration of pulses on the exit lens and the delay between the pulses on the exit lens and the extraction pulses on the TOF also increase with mass. A complete product ion spectrum, which is enhanced over a wide mass range, can be obtained by adding the resulting sections of the spectrum together. This algorithm was demonstrated in an MS/MS experiment with the peptide ALILTLVS.

In the work of Chernushevich and Thomson, a linear ion trap was used to increase duty cycle and ion intensity only. The capability of "tandem in time MS" in a linear ion trap was not explored. Cousins & Thomson (2002) showed that fragment ions formed in the collision cell could be excited to cause additional fragmentation. Subtraction of spectra gave MS^3 and MS^4 spectra. No ion isolation or trapping in the collision cell was used, but these could be applied in a straightforward manner.

Wang and co-workers developed a dual linear ion trap TOF mass spectrometer system (Wang et al., 2001, 2002; Wang, Park, & Giessmann, 2002). There are three sets of multipoles in the system: a linear hexapole ion trap, a mass resolving quadrupole, and a linear quadrupole ion trap. In MS/MS mode, ions generated by ESI are accumulated in the linear hexapole ion trap. Precursor ions are then selected by the mass resolving quadrupole and enter the linear quadrupole ion trap with a kinetic energy determined by the potential difference between the hexapole and quadrupole ion traps. The linear ion trap acts as a collision

cell for ion fragmentation. Thus triple quadrupole-like spectra that access higher energy dissociation channels than 3D trap MS/MS spectra should be possible. Fragment ions are confined in the trap, cooled through subsequent collisions, pulsed out of the trap in a timed release method, focused by ion optics, and mass analyzed by an orthogonally coupled TOFMS. This system also improves the overall duty cycle. When the first ion packet leaves the first trap and enters the mass resolving quadrupole, the first ion trap can accumulate a second ion packet. Furthermore, ions leaving the second trap can be emptied by gating the potential on the exit electrode of the second trap for a relatively long time before the next ion packet refills the second trap. Therefore, ions from the previous packet do not contribute to the spectra of the next ion packet, eliminating cross contamination or memory effects. Fragmentation of reserpine (Wang, Park, & Giessmann, 2002) and [Glu^1] fibrinopeptide B (Wang et al., 2001) was demonstrated. Again, it is possible to apply ion isolation and fragmentation using resonant excitation in the collision cell to obtain MS^n spectra in this system.

C. Linear Traps Combined with FTICR

Linear traps can be used to improve the performance of FTICR (or FTMS) systems. As with 3D ion traps, the duty cycle can be increased to nearly 100% if ions are accumulated in a linear trap, while the FTMS performs other functions (Senko et al., 1997). Unwanted ions that can cause space charge problems in the FTMS can be ejected in the linear trap to improve the resolution, sensitivity, and dynamic range of the system.

For high mass resolution, FTMS requires a base pressure of ca. 1×10^{-8} Torr in the ICR cell (Henry & McLafferty, 1990). One method to increase the ion trapping efficiency in the FTMS of externally generated ions is to apply a timed gas pulse (Beu et al., 1993), which reduces the ions' kinetic energies by collisional cooling. This requires a pump down delay of several seconds before mass analysis (Senko et al., 1997). With cryogenic pumps, the gas pulse can overload the pumps resulting in reduced pump speeds (Belov et al., 2001c) and also requires more frequent time-consuming pump regeneration. A linear ion trap can be separated from the high vacuum chamber of the FTMS and operated at higher pressures to accumulate and collisionally cool ions before they are injected into the FTMS. The need for a gas pulse in the FTMS can be eliminated, reducing the gas load on the high vacuum system and increasing the analysis speed (Senko et al., 1997).

Marshall's group (Senko et al., 1997) described a linear octopole ion trap coupled to a FTMS; earlier, Pope et al. (1997) had described external ion accumulation in a hexapole trap; however, details regarding the trap were not

provided. Other groups soon followed by incorporating linear multipole traps into their FTMS systems. In Marshall's instrument, ions are trapped in a 60 cm linear octopole ion guide operated at $\sim 10^{-2}$ Torr (Senko et al., 1997); significant increases in sensitivity were reported. For 500 fmol of arg^8-vasotocin, met-enkephalin, and β-casomorphin, separated on-line by nano-liquid chromatography (LC), and with ions accumulated in the linear ion trap for 3 sec, a sensitivity increase of $\sim 20,000\times$ over the "best" published result was found. A nonlinear increase in ion intensity was observed for increasing ion accumulation times. This was attributed to a "Coulombically assisted trapping mechanism" (Senko et al., 1997). Belov et al. (2001b) made similar observations and found that the intensity of leucine enkephalin ions, $(M + 1H^+)^{1+}$, increased $\sim 10\times$ for an ion injection time that was only $6.25\times$ greater. For the same number of ions in the FTMS, the time-domain signal decayed ca. $10\times$ more slowly when ions were accumulated in a linear trap (Senko et al., 1997). This improved resolution and sensitivity. For ubiquitin, the maximum resolving power obtained for conventional internal ion accumulation and ion accumulation in a linear trap were $\sim 2.5 \times 10^5$ and $> 10^6$, respectively (Senko et al., 1997).

Wilcox, Hendrickson, & Marshall (2002) added angled wires (relative to the z-axis) between the rods in a linear octopole trap. By applying a DC potential to the wires, an axial electric field was produced, and ions were ejected from the linear trap more rapidly. An improvement in the S/N of ~ 14 was observed for the extraction of bovine ubiquitin ions.

Hofstadler and co-workers (Sannes-Lowery et al., 1998) used a linear hexapole ion trap. A timed potential applied to an exit electrostatic lens and a constant DC potential applied to an inlet skimmer were used to trap ions. A solenoid-activated shutter was later added to allow a more thorough characterization of the ion dynamics in the linear trap (Hofstadler, Sannes-Lowery, & Griffey, 1999a). Infrared multiphoton dissociation (IRMPD) in the linear trap was demonstrated (Hofstadler, Sannes-Lowery, & Griffey, 1999a; Griffey & Hofstadler, 2000; Hofstadler & Griffey, 2002). An unfocused, 25 W continuous wave CO_2 laser beam, centered on the axis of both the linear trap and the FTMS cell, dissociated ions in either region. For ions of a 20-mer phosophorothioate oligonucleotide accumulated and concurrently irradiated in the linear trap for 500 msec, less fragmentation was observed than with in-cell (FTMS) IRMPD (100 msec irradiation). The in-cell dissociation was dominated by low m/z singly charged ions. Dissociation in the external hexapole trap gave a greater range of fragment ions, more multiply charged fragment ions, greater sequence coverage, improved mass resolution, and improved sensitivity. The greater sequence coverage was attributed to two causes: (1) all ions in the linear trap were

not irradiated for the same duration and therefore, for some ions, less 'heating' occurred to promote fragmentation; (2) the pressure in the linear trap was *ca.* 1,000× greater (10^{-6} Torr) than in the FTMS. The higher pressure gas collisionally deactivated metastable trapped ions that otherwise would have undergone further fragmentation.

As described above, a linear ion trap can be used to study ion-molecule reactions such as H/D exchange at relatively high pressure. Hofstadler, Sannes-Lowery, & Griffey (1999b, 2000) measured H/D exchange levels of ions of several biomolecules in a linear hexapole ion trap with mass analysis by FTMS. In a first set of experiments, ion accumulation and exchange occurred simultaneously so that exchange times were not well defined (Hofstadler, Sannes-Lowery, & Griffey, 2000). Ions were trapped for 0–30 sec and subjected to continuous infusion of D_2O vapor. For cytochrome-*c* ions $(M + 12H^+)^{12+}$, H/D exchange with D_2O gave a bimodal distribution of 77 and 96 exchanges after ~5 sec. Exchange appeared complete after 30 sec, with 92 and 115 exchanges. This exchange was reported as 100× faster (Hofstadler, Sannes-Lowery, & Griffey, 2000) than previously published FTMS in-cell exchange with D_2O at 10^{-7} Torr (Suckau et al., 1993). In later experiments (Hofstadler, Sannes-Lowery, & Griffey, 1999b, 2000), a mechanical shutter was used to gate ions into the trap so that the exchange time was well defined. H/D exchange of cytochrome-*c* $(M + 14H^+)^{14+}$ ions was demonstrated to be nearly complete with 88 exchanges in 5 sec. Back exchange with atmospheric gases and ESI solvents was observed and could be reduced by placing a seal over the inlet system.

Smith's group developed a linear quadrupole ion trap that is divided into 22 individual segments (Belov et al., 2001c) to provide an axial field to eject ions. Belov et al. (2001a) proposed that without the axial field, ion ejection from a conventional linear trap proceeds through a charge repulsion mechanism. By matching the time required to empty the trap to the gated trapping event, most ions are efficiently trapped in the FTMS (Belov et al., 2001a,f). The multi-segmented linear trap with an axial electric field of 0.3 V cm^{-1} allowed for ejection of all ions in 400 μsec (Belov et al., 2001a). With the linear ion trap for external ion accumulation, ions from a 1×10^{-12} M solution of *cytochrome-c* infused for 5 sec at 300 nL min^{-1} (2.5×10^{-20} moles consumed) were detected (Belov et al., 2001a), and for external ion accumulation in a linear ion trap, the sensitivity was ~5× higher than for standard in-cell (FTMS) ion accumulation (Belov et al., 2001a).

Typically ~100 charges of a given *m/z* are needed to produce an image current for quantitation in an FTMS (Belov et al., 2001b). If the overall dynamic range of the FTMS, limited by the minimum space charge required to induce coalescence (Anderson & Laude, 1996; Belov et al., 2001b), is ~10^3 (Belov et al., 2001g; Paša-Tolić et al.,

2002), this will limit the total number of ions that can be mass analyzed. Regulatory proteins can be expressed at <1,000 per cell while more abundant proteins may be expressed at >10^6 per cell (Paša-Tolić et al., 2002). As a consequence, for proteomics applications, low ion currents can be masked by high ion currents (Paša-Tolić et al., 2002).

Smith's group demonstrated a data-dependent ion isolation method for enhancing the dynamic range of the FTMS (Belov et al., 2001f,g; Belov, Anderson, & Smith, 2002; Harkewicz et al., 2002; Paša-Tolić et al., 2002). This technique, named DREAMS (dynamic range expansion applied to mass spectrometry), functions as follows. Ions are mass analyzed by the FTMS and a data processor identifies ions with high intensities. An auxiliary excitation waveform, containing frequencies corresponding to the secular frequencies of motion (Eq. 2.17) for these ions, is applied to a nontrapping selection quadrupole. The most abundant ions are resonantly ejected by dipolar excitation from a second packet of ions and the remaining ions are accumulated in the linear trap. The linear trap is then emptied into the FTMS and a second mass spectrum is obtained (Belov et al., 2001g).

More low-intensity bovine serum albumin (BSA) tryptic digest peptide ions were identified using DREAMS than with conventional FTMS techniques (Belov, Anderson, & Smith, 2002). The increased sensitivity was attributed to the selective accumulation, for an extended period, of peptide ions of low abundance (Belov, Anderson, & Smith, 2002). Using conventional FTMS techniques, quantitative analysis of *all* tryptic peptides from mouse B16 melanoma cells using $^{14}N/^{15}N$ metabolic labeling, produced 9,896 $^{14}N/^{15}N$ peptide pairs (Paša-Tolić et al., 2002). Using DREAMS to remove the most abundant ions, 8,856 $^{14}N/^{15}N$ peptide pairs were identified, of which 7,917 were newly identified. Therefore the total number of "unambiguous and unique peptide pairs" found was 17,813 (Paša-Tolić et al., 2002). While the dynamic range is improved using DREAMS, the mass accuracy decreases, probably because of varying charge densities in the FTMS (Belov, Anderson, & Smith, 2002). It was proposed that an external mass calibrant could improve the mass accuracy (Belov, Anderson, & Smith, 2002). This technique is likely to benefit other ion trap mass spectrometers.

For LC, mass spectrometry, Belov et al. (2003) described a feedback mechanism that automatically adjusts the ion injection time to prevent space charge problems in the linear and FTMS traps. A pre-scan mass spectrum (similar to DREAMS) is obtained and based on the total ion signal chromatogram (the sum of the ion intensities for a range of *m/z*) the ion injection time is adjusted to allow similar numbers of charges to be accumulated in the linear trap. The total ion signal chromatogram is used in the feedback loop rather than the total ion current, measured on

either a conductance limit prior to the FTMS or on a plate at the rear of the FTMS, because the correlation between the total ion current and the total ion signal chromatogram is poor (Belov et al., 2003).

Baykut and co-workers (Baykut & Franzen, 2000; Baykut, Jertz, & Witt, 2000) described the use of a linear hexapole ion trap to couple a MALDI source to an FTMS system. Because of the large kinetic energy variation associated with ions generated by MALDI (Juhasz, Vestal, & Martin, 1997), ions were cooled in the trap with a 0.5 sec pulse of Ar. The MALDI target plate was the linear trap entrance electrode, whereas an aperture plate was used as the exit lens. To increase sensitivity, ions generated in multiple laser shots could be accumulated in the trap. The sensitivity was demonstrated with substance P; with 200 attomoles placed on the sample plate, a S/N ratio of 133 was achieved at a resolution of 300,000. With broadband detection, a S/N of 16 was achieved with just 10 attomoles deposited on the plate. Tandem mass spectrometry of ions of luteinizing hormone releasing hormone was demonstrated along with identification of bovine serum albumin from ions of peptides from a tryptic digest placed on the plate.

H/D exchange in a linear hexapole trap of 10 different peptide ions generated by MALDI, combined with FTMS, was described by Witt, Fuchser, & Baykut (2002). After ions were cooled with Ar, the deuterating agent CD_3OD or D_2O was added and ions exchanged for up to 60 sec. As described above, because of the higher gas pressure in the linear trap, the reaction rate is much greater than in the FTMS cell, the gas load on the FTMS system is reduced, and the resolution in the FTMS is improved. Formation of a dimer between ions of substance P and triethlyamine was also observed. Ions of the dimer could be dissociated by IRMPD. Accumulation of ions in a linear trap from a MALDI source is not limited to FTMS. Other mass analyzers may benefit from this technique.

the rods within 200 μm accuracy. To reduce inhomogeneities in the field, the sensing electrodes are pulled back from the center of the trap. The end and central sections of the detection electrodes are 1 and 4 inches long, respectively. Ions are confined axially by potentials on the end sections. In each ion measurement cycle, voltages on the front ends of the sensing electrodes are reduced to allow ions from the previous measurement to escape from the trap. The voltage on the entrance lens then decreases, and ions, accumulated in an upstream octopole trap, are transferred into the analyzing trap. The RF voltage on the rods is ramped to a higher level for mass analysis. Ions are then excited to an amplitude of approximately 50% of the radius of the trap, and image currents are measured on the detection electrode with a detection efficiency of ≈20%. Before the primary excitation, an initial pulse can be added to decouple isotopic peaks. A resolving power of 7,500 at $m/z = 69$ from FC-43 was shown (Senko et al., 2000). Although the results are promising, the mass range reported was reported to be approximately 400 (Senko, 2002). As with other traps, the performance is also limited by space charge effects. The image current measurement required so many ions that space charge effects could not be avoided (Schwartz, Senko, & Syka, 2002b).

B. Linear Quadrupole Ion Trap Mass Spectrometer with Radial Ion Ejection

In 1995, Bier, Park, & Syka (1995) proposed increasing the volume of a trap by using a linear quadrupole trap, with mass selective radial ejection, as a stand-alone mass spectrometer. These ideas were later explored by Schwartz and co-workers (Schwartz, Senko, & Syka, 2002a,b; Senko & Schwartz, 2002). Figure 9 shows the electrodes of a linear quadrupole ion trap mass spectrometer with radial ion

IV. LINEAR TRAPS AS MASS SPECTROMETERS

A. Fourier Transform Mass Spectrometry in a Linear Quadrupole Ion Trap

Fourier transform mass spectrometry in a linear quadrupole ion trap has been proposed (Senko et al., 2000; Senko, 2002). Ions in the trap are excited into coherent motion, and the image current is detected for Fourier analysis. Detecting the weak image current in the presence of the high RF trapping field is challenging. The proposed trap has a field radius, r_0, of 20 mm with four flat surface rods (Senko, 2002). An approximately quadrupole electric field is created in the inner 50% of the trap. Four three-segmented sensing electrodes, 1.4 mm thick, are interleaved between
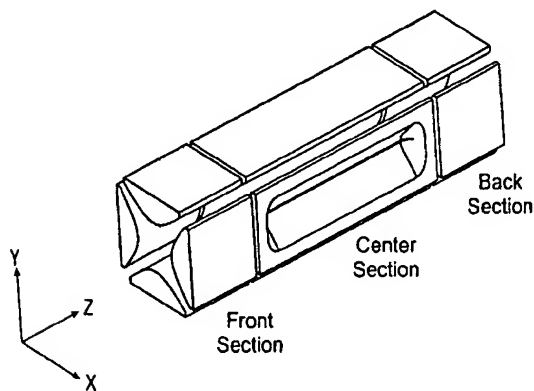

FIGURE 9. The electrodes of a linear quadrupole ion trap mass spectrometer. Reproduced with permission from Schwartz, Senko, & Syka (2002b). Copyright 2002 Elsevier.

ejection (Schwartz, Senko, & Syka, 2002b). Hyperbolic rods are cut into three sections of 12, 37, and 12 mm length, respectively. These rods are positioned adjacently to avoid fringe field distortions of the trapping and excitation fields. Ions are confined radially in the central section by the RF voltage (up to ± 5 kV pole-to-ground, 1 MHz, corresponding to a mass range of 2,000 with resonant ejection for mass analysis at a q of 0.88) and axially by DC potentials on the end sections. Ions are extracted through a 30 × 0.25 mm slot in a rod in the direction of the x axis (an "X rod"). The ion detection efficiencies can be doubled if ions are extracted through both X rods provided two detectors are used (Senko & Schwartz, 2002). To compensate for the field distortions induced by the slots in the X rods, these rods are moved out 0.75 mm from the center. Ions are detected by a conversion dynode (-15 kV for positive ions) and an electron multiplier. Dipole excitation with auxiliary AC voltages on the X rods is used to isolate, excite, and eject ions. Ions are isolated by a broadband waveform with frequencies 5–500 kHz spaced every 500 Hz, with a notch at the frequency of the target ions (typically at $q = 0.83$). Ions are activated by resonant excitation at a q of 0.25–0.35 to give a compromise between fragmentation and confinement.

The storage space charge ion capacity, that is, the maximum number of ions stored was estimated to be 7×10^6, whereas the spectral space charge ion limit, that is, the maximum number of stored ions sufficient to obtain a mass spectrum with a given mass resolution and accuracy was around 2×10^4 (Schwartz, Senko, & Syka, 2002a). These values are more than ten times higher than those of a 3D ion trap. The increased ion capacity, and the higher ion injection efficiency, compared to a 3D trap, increased sensitivity. This was demonstrated with a 500 fg sample of alprazolam, analyzed by LC/MS/MS ($m/z = 309 \rightarrow 274$). The detection limit was five times lower than the detection limits with a 3D ion trap (Schwartz, Senko, & Syka, 2002b). A mass resolution of greater than 30,000 at a reduced scan rate of 27 amu sec^{-1} was obtained, and MS^4 was demonstrated (Schwartz, Senko, & Syka, 2002a).

C. Linear Quadrupole Ion Trap Mass Spectrometer with Axial Ejection

In a series of patents (Hager, 2001, 2002b, 2003a,b) and studies (Hager, 1998, 1999, 2002a), Hager has described how ions can be ejected axially from a linear quadrupole ion trap in a mass selective manner. The method is based on earlier experiments, first discussed by Brinkmann (1972), which produce mass spectra from RF-only quadrupoles (i.e., with no resolving DC applied between the rods). Ions flow through an RF-only quadrupole without trapping. Ions with q values close to the stability boundary limit ($q = 0.908$) receive increased energy in the x and y

directions. The fringing field near the quadrupole exit couples these x and y motions to the axial motion, and ions overcome a stopping potential barrier applied at the quadrupole exit. Mass spectra are produced by scanning the amplitude of the RF voltage to bring ions of different m/z ratios to the stability boundary. Because only ions in the fringing field are ejected, it is possible to build a very short mass analyzing quadrupole. Hager (1999) demonstrated unit resolution at $m/z = 354$ and 609 with a mass analyzer only 24 mm long. The resolution was improved by unbalancing the RF and applying a small resolving DC voltage between the rods. The sensitivity and resolution were also improved by applying an auxiliary voltage at the frequency of the quadrupole RF to the exit aperture.

Similar principles were then used to eject trapped ions axially from a linear quadrupole (Hager, 2001, 2002a). The apparatus is shown in Figure 10 (Hager, 2002a). A triple quadrupole mass spectrometer was used and ions could be trapped in either q2 (operated at a pressure of $\geq 1 \times 10^{-4}$ Torr) or Q3 (operated at $\sim 3 \times 10^{-5}$ Torr) by applying stopping potentials to aperture plates at the ends of the quadrupoles. Ions, excited at their resonant frequencies in the region near the trap exit, accumulate kinetic energy. The fringing fields mix the motions in the x, y, and z directions, and ions gain sufficient kinetic energy to overcome the stopping potential at the trap exit. Excitation can be applied to the exit aperture, as dipole excitation between a pair of rods, or as quadrupole excitation. By changing the excitation frequency, ions of different m/z can be ejected to produce a mass spectrum. Alternatively, the excitation frequency can be fixed and the trapping RF scanned to bring ions of different m/z ratios into resonance. It was found to be advantageous to increase the RF excitation voltage proportional to the m/z value of the ion being ejected.

First experiments (Hager, 2002a) were done with ions trapped in q2 (4×10^{-4} Torr) and with quadrupole excitation. Approximately, unit mass resolution was obtained
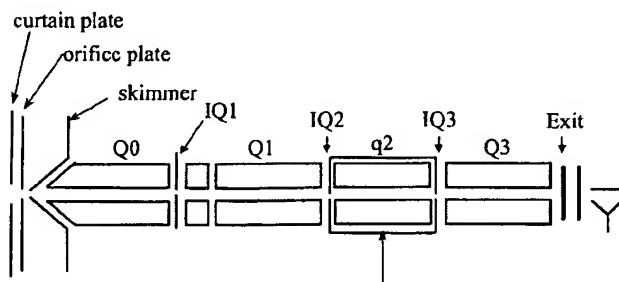
FIGURE 10. A triple quadrupole mass spectrometer with axial ejection of trapped ions. Reproduced with permission from Hager (2002a). Copyright 2002 John Wiley & Sons Limited.

at $m/z = 609$. Trapping efficiencies depended on the cell pressure and q values of the trapped ions. A q of 0.4 gave the highest trapping efficiencies, from 58% to 95%. The extraction efficiency was also found to depend on the pressure, and ranged from 2% to 18% (ions of $m/z = 609$). Because it is the fringing fields, which cause ion ejection, only ions in the last $ca. 5r_0$ of the quadrupole are ejected. The remaining ions are lost to the rods. For MS/MS, the linear trap q2 could, in principle, be operated as in the linear trap-TOF system described above (Section V), with ion injection, ion isolation with tailored waveforms, excitation to induce dissociation, and axial ejection of fragment ions to produce a mass spectrum. However, because the instrument is based on the ion path of a triple quadrupole system, new scans and methods of producing MS/MS spectra are possible. Precursor ions can be selected by Q1 in the normal fashion, and injected into q2 with sufficient energy to cause fragmentation; ions can then be ejected axially to produce a mass spectrum of fragment ions. The advantages include an increased duty cycle, MS/MS spectra similar to those of a triple quadrupole that include higher-energy channel fragment ions than 3D trap MS/MS spectra, and reduction of space charge problems because only precursor ions selected in Q1 are injected into the trap (Hager, 2002a, 2003b). The sensitivity of the system (Hager, 2002a) for fragments of reserpine ions with trapping in Q2 was compared to conventional MS/MS mode. The sensitivity was $ca.$ 12 times greater when fragment ions were trapped and then ejected axially, because of a greater duty cycle. Because the instrument can be operated as a conventional triple quadrupole system, neutral loss, precursor ion scans, and single and multiple reaction monitoring (SRM and MRM) are possible.

The resolution with axial ejection from q2 (4×10^{-4} Torr) was typically $R_{1/2} = 1,000$ at $m/z = 609$ with a scan rate of 1,000 Th sec^{-1}. With slower scans, the resolution increased, and a resolution of $R_{1/2} = 6,000$ at $m/z = 609$ was demonstrated with a scan speed of 5 Th sec^{-1}. Additional experiments were done with axial ejection of ions from Q3. It was found that, because of the lower pressure in Q3 (3×10^{-5} Torr), $R_{1/2} = 6,000$ could be obtained at a scan speed of 100 Th sec^{-1}. Thus, a $20\times$ greater scan speed than that in q2 gave the same resolution (Hager, 2002a). An MS/MS experiment was also done with fragment ions trapped and then axially ejected from Q3. The full scan sensitivity was $16\times$ greater than that of a conventional triple quadrupole MS/MS scan, and higher resolution was possible. In later experiments, it was shown that similar experiments could be used to improve the sensitivity of a QqTOF system, particularly for precursor and neutral loss scans (Hager, 2003b).

Hopfgartner, Husser, & Zell (2003) have described first applications of the linear trap system of Figure 10 in drug discovery, including the analysis of trocade and

tolcapone in urine, the analysis of remkiren in rat hepatocytes and the analysis of an amine of unspecified structure in dog plasma. Fragment ions were formed in q2, trapped in Q3, and then axially ejected to give an LC-MS/MS spectrum. The higher collision energies of MS/MS in q2 allowed production of a greater range of fragment ions than could be formed in a 3D ion trap. The same fragments could be produced in a 3D trap by MS^n, although this slowed the analysis. Trapping fragment ions in Q3 followed by axial ejection increased the sensitivity of MS/MS by a factor of 60 compared to running MS/MS in the normal triple quadrupole mode on the same instrument.

Conventional product ion scans and product ion scans with fragments trapped in Q3 were compared. For quantitative LC/MS of metabolites of an amine in dog plasma, the same instrument was operated as a conventional triple quadrupole MS/MS system and showed a linear dynamic range of four orders of magnitude. Because of the high duty cycle, up to eight experiments could be performed on a peak in a single chromatographic run. Approaches to "information dependent data" acquisition with this new instrument were discussed (Hopfgartner, Husser, & Zell, 2003).

Leblanc et al. (2003) described applications to proteomics. Identification of six phosphorylated peptides in a mixture was attempted by looking for loss of $m/z = 79$ (PO_3) in a negative mode neutral loss scan. Once candidate ions were identified, the instrument was switched to positive mode, high resolution scans of ions trapped in Q3 were used to identify charge states, followed by MS/MS scans with fragments trapped and mass analyzed in Q3 (total cycle time 4.3 sec). Four of six peptides at a concentration of 50 fmol μL^{-1} were identified. The system was also operated to search for neutral loss of 49 (i.e., mass 98 (H_3PO_4) from doubly charged ions) in positive ion mode. The duty cycle improved because it was not necessary to switch the system polarity. A method of increasing the levels of multiply charged ions relative to singly charged ions that form chemical noise was described. Ions were trapped in Q3 and collisionally cooled. The trapping exit barrier was lowered and singly charged ions were preferentially released (Hager, 2002b; Leblanc et al., 2003). Multiply charged peptide ions were readily identified under conditions where none could be identified without this enhancement of the multiply charged ions. Application of this technique to a QqTOF system with ions confined in the collision cell is described by Chernusevich et al. (2003).

V. SUMMARY AND OUTLOOK

New applications for linear traps are being found and linear traps have already been incorporated in several commercial

instruments. Improvements in instrument performance can be expected. For example, in all the work cited above, resonant excitation of ions in linear quadrupole traps showed relatively low resolution ($R_{1/2} < 300$). In part, this can be attributed to the relatively high pressures used ($>4 \times 10^{-4}$ Torr), which require greater excitation voltages. Recently, Collings, Stott, & Londry (2003) have demonstrated a resolution of $R_{1/2} = 1200$ for excitation of protonated reserpine ions in a linear quadrupole trap at a pressure of 3×10^{-5} Torr. Excitation times of 100 msec were necessary. Despite the comparatively low pressure, the fragmentation efficiency could be as high as 90%.

It is well established that 3D traps benefit from stretched or other geometries that introduce field distortions, described by the addition of higher order multipoles to the potential (e.g., Franzen et al., 1995). Addition of a positive octopole component to the field in the z direction of a 3D trap can improve MS/MS efficiency, and give faster ejection of ions at the stability boundary (Franzen et al., 1995; Sudakov, 2001) leading to faster scan speeds and improved mass resolution. Adding a positive octopole field in the direction of ejection of ions from a linear quadrupole trap (Fig. 9) could be expected to provide the same improvements. Methods to add an octopole field in the range 0.1% to 10% to a linear quadrupole field have been described very recently (Sudakov & Douglas, 2003). By making one set of round rods (say the y rods) larger in diameter than the other pair (x rods), an octopole component can be added, whereas contributions from other higher order multipoles remain small. In view of the previous literature on the need to keep higher order multipoles very small in linear quadrupoles used as conventional mass filters (Dawson & Whetton, 1969; Dawson, 1980), it would not be expected that quadrupoles with added octopole fields of 1–4% could be used as mass filters. Surprisingly, they can provide mass resolution comparable to conventional rod sets provided the polarity of the DC applied to the rods is correct. For mass analysis of positive ions, the positive DC should be applied to the smaller rods (Ding, Konenkov, & Douglas, 2003). Thus for instruments where the same rod set must be used both as a trap with resonant excitation and as a mass filter (Fig. 10), a quadrupole with added octopole may improve trap performance and still allow conventional mass analysis. First measurements of frequency shifts in excitation, MS/MS efficiencies, and nonlinear resonances with a linear quadrupole ion trap with 4% added octopole field have been reported (Frank & Douglas, 2003). Much work remains to be done to explore methods of adding higher multipoles to linear quadrupole rod sets, and to investigate the effects of these multipoles on the performance of the rod sets as traps and mass filters. Finally, when linear traps have a curved axis, additional multipoles are added to the potential. Lammert et al. (2000) have described an improved

electrode geometry for a toroidal quadrupole trap, and further optimization of the geometry for such traps remains to be explored.

ACKNOWLEDGMENTS

VI. LIST OF SYMBOLS

∇	gradient operator
α	proportionality constant
β	stability parameter
ξ	$\Omega \cdot t/2$
ε_0	permittivity of free space (8.85×10^{-12} Nm^{2}C^{-2})
ζ	complex variable, $x + iy$
θ	angle
λ	damping constant
μL	microliter
μM	micromolar
σ	cross-sectional area of an ion (collision cross section)
φ_N	multipole of order N
$\phi_N(x,y)$	potential of a 2D multipole of order N
$\Phi(x,y)$	2D electric potential
$\Phi(x,y,t)$	2D time-dependent potential
$\Psi(t)$	time-dependent potential applied pole to ground
ω_n	angular frequency of ion oscillation
ω_{ex}	excitation frequency
ω_j^K	quadrupole excitation frequency
ω_0	frequency of a harmonic oscillator
Ω	angular frequency of RF applied to a multipole
2D	two-dimensional
3D	three-dimensional
A	constant
a	Mathieu parameter
AC	alternating current
amu	atomic mass unit
A_N	amplitude of a multipole of order N
B	constant
C_d	drag coefficient
$D_{x,y}$	effective potential well depth in a linear quadrupole
D_z	effective potential well depth for z motion in a 3D Paul trap
DC	direct current
e	magnitude of the electron charge
eV	electron volt

$\vec{E}$ electric field
$\vec{F}$ force
f frequency
F_d drag force
f_{ex} threshold force for parametric excitation
fmol femtomole
FNF filtered noise field
FTICR Fourier transform ion cyclotron resonance
FTMS Fourier transform mass spectrometry
fwhm full width at half maximum
H^+ proton
Hz Hertz
i $i^2 = -1$
j $j = 0, \pm 1, \pm 2 \ldots$
IRMPD infrared multiphoton dissociation
K positive integer, $K = 1, 2, 3, \ldots$
l length
l_c ion cloud length
LC liquid chromatography
LIT linear ion trap
m meter
m ion mass
m/z mass to charge ratio
m_0 collision gas mass
MSAD multipole storage assisted dissociation
MALDI matrix-assisted laser desorption ionization
MCP micro channel plate
MRM multiple reaction monitoring
MS mass spectrometry
MS^n ion isolation and fragmentation with n steps of mass selection
n integer
n_g gas number density
n_i ion density
$n_{i,max}$ maximum number of ions that can be stored in a trap
N order of a multipole
N_{2D} number of ions stored in 2D ion trap
N_{3D} number of ions stored in 3D ion trap
PEG poly(ethylene glycol)
PPG poly(propylene glycol)
Q mass resolving quadrupole
q RF only quadrupole
q Mathieu parameter
r radial distance
r_0 field radius
$R_{1/2}$ resolution, fwhm
R_{2D} radius of a cylindrical ion cloud
R_{3D} radius of the ion cloud in a 3D trap
r_e electrode radius
RF radio frequency
R_{sph} radius of a spherical ion cloud
sec second

S/N signal to noise ratio
SRM single reaction monitoring
SWIFT stored waveform inverse Fourier transform
t time
$T_{A,2D}$ time to process ions in a linear trap
$T_{A,3D}$ MS analysis time, 3D trap
$T_{A,LIT}$ Time, process in LIT
T_E time to empty a linear trap into a 3D trap
T_L ion collection time in a linear trap
Th Thomson
TOF time of Flight
U DC potential pole to ground
U_{eff} effective mechanical potential
$\vec{v}$ ion velocity
V_{aux} zero to peak auxiliary RF potential, pole to ground
V_{eff} effective electric potential
V_{RF} radio frequency voltage, pole to ground
x Cartesian co-ordinate
y Cartesian co-ordinate
z Cartesian co-ordinate or number of charges on an ion
z_0 center to end cap distance in a 3D ion trap

REFERENCES

Anderson JS, Laude DA. 1996. Experimental methods to alleviate ion coupling effects in matrix-assisted laser desorption ionization Fourier transform ion cyclotron resonance mass spectrometry. Int J Mass Spectrom Ion Processes 157(158):163–174.

Baykut G, Jertz R, Witt M. 2000. Matrix-assisted laser desorption/ionization Fourier transform ion cyclotron resonance mass spectrometry with pulsed in-source collision gas and in-source ion accumulation. Rapid Commun Mass Spectrom 14:1238–1247.

Baykut G, Franzen J. 2000. Method and device for controlling the filling of ions into an icr mass spectrometer. UK Pat. Appl. 2353632.

Beaugrand B, Devant D, Jaouen D, Mestdagh H, Rolando C. 1987. Ion confinement in the RF-only collision cell of a tandem quadrupole instrument. Spectros Int J 5:265–272.

Beaugrand C, Jaouen J, Mestadagh H, Rolando C. 1989. Ion confinement in the collision cell of a multiquadrupole mass spectrometer: Access to chemical equilibrium and determination of kinetic and thermodynamic parameters of an ion-molecule reaction. Anal Chem 61:1447–1453.

Belov ME, Anderson GA, Smith RD. 2002. Higher-resolution data-dependent selective external ion accumulation for capillary LC-FTICR. Int J Mass Spectrom 218:265–279.

Belov ME, Nikolaev EN, Anderson GA, Udseth HR, Conrads TP, Veenstra TD, Masselon CD, Gorshkov MV, Smith RD. 2001a. Design and performance of an ESI interface for

selective external ion accumulation coupled to a FTICR MS. Anal Chem 73:253–261.

Belov ME, Nikolaev EN, Anderson GA, Auberry KJ, Harkewicz R, Smith RD. 2001b. Electrospray ionization-FTICR MS using ion preselection and external accumulation for ultrahigh sensitivity. J Am Soc Mass Spectrom 12:38–48.

Belov ME, Nikolaev EN, Harkewicz R, Masselon CD, Alving K, Smith RD. 2001c. Ion discrimination during ion accumulation in a quadrupole interface external to a FTICR MS. Int J Mass Spectrom 208:205–225.

Belov ME, Gorshkov MV, Udseth HR, Smith RD. 2001d. Controlled ion fragmentation in a 2-D quadrupole ion trap for external ion accumulation in ESI FTICR MS. J Am Soc Mass Spectrom 12:1312–1319.

Belov ME, Gorshkov MV, Alving K, Smith RD. 2001e. Optimal pressure conditions for unbiased external ion accumulation in a 2-D radio-frequency quadrupole for FTICR MS. Rapid Commun Mass Spectrom 15:1988–1996.

Belov ME, Nikolaev EN, Alving K, Smith RD. 2001f. A new technique for unbiased external ion accumulation in a quadrupole 2-D ion trap for ESI FTICR MS. Rapid Commun Mass Spectrom 15:1172–1180.

Belov ME, Anderson GA, Angell NH, Shen Y, Tolic N, Udseth HR, Smith RD. 2001g. Dynamic range expansion applied to mass spectrometry based on data-dependent selective ion ejection in capillary liquid chromatography FTICR for enhanced proteome characterization. Anal Chem 73:5052–5060.

Belov ME, Rakov VS, Nikolaev EN, Goshe MB, Anderson GA, Smith RD. 2003. Initial implementation of external accumulation liquid chromatography/electrospray ionization Fourier transform ion cyclotron resonance with automated gain control. Rapid Commun Mass Spectrom 17:627–636.

Beu SC, Senko MW, Quin JP, McLafferty FW. 1993. Improved fourier-transform ion-cyclotron-resonance mass spectrometry of large biomolecules. J Am Soc Mass Spectrom 4:190–192.

Bier ME, Park M, Syka JEP. 1995. Ion trap mass spectrometer system and method. US Patent 5,420,425.

Brinkmann U. 1972. Modified quadrupole mass filter for the separation of ions of higher masses with high transmission. Int J Mass Spectrom Ion Phys 9:161–166.

Campbell JM, Collings BA, Douglas DJ. 1998. A linear ion trap time-of-flight system with tandem mass spectrometry capabilities. Rapid Commun Mass Spectrom 12:1463–1474.

Cha B. 2002. An interface with a linear quadrupole ion guide for an electrospray ion trap mass spectrometer system. Ph. D. Thesis, University of British Columbia.

Cha B, Blades M, Douglas DJ. 2000. An interface with a linear quadrupole ion guide for an electrospray-ion trap mass spectrometer system. Anal Chem 72:5647–5654.

Chen Y-L, Collings BA, Douglas DJ. 1997. Collision cross sections of myoglobin and cytochrome c ions with Ne, Ar, and Kr. J Am Soc Mass Spectrom 8:681–687.

Chen Y-L, Campbell JM, Collings BA, Konermann L, Douglas DJ. 1998. Stability of a highly charged noncovalent complex in the gas phase: Holomyoglobin. Rapid Commun Mass Spectrom 12:1001–1010.

Chernusevich IV, Fell LM, Bloomfield N, Metalnikov PS, Loboda AV. 2003. Charge state separation for protein applications using a quadrupole time-of-flight mass spectrometer. Rapid Commun Mass Spectrom 17:1416–1424.

Chernushevich IV. 2000. Duty cycle improvement for a quadrupole-time-of-flight mass spectrometer and its use for precursor ion scans. Eur J Mass Spectrom 6:471–479.

Chernushevich I, Thomson B. 1999. MS/MS scan methods for a quadrupole/time of flight tandem mass spectrometer. Eur Patent Appl 99303754.8.

Chernushevich I, Thomson B. 2001. MS/MS scan methods for a quadrupole/time of flight tandem mass spectrometer. US Patent 6,285,027.

Chernushevich I, Thomson B. 2002. MS/MS scan methods for a quadrupole/time of flight tandem mass spectrometer. US Patent Appl 09/864,872.

Chernushevich I, Thomson B. 2003. MS/MS scan methods for a quadrupole/time of flight tandem mass spectrometer. US Patent 6,507,019.

Chien BM, Micheal SM, Lubman DM. 1994. The design and performance of an ion trap storage-reflectron time-of-flight mass spectrometer. Int J Mass Spectrom Ion Processes 131:149–179.

Church DA. 1969. Storage-ring ion trap derived from the linear quadrupole radiofrequency mass filter. J Appl Phys 40:3127–3134.

Collings BA, Stott WR, Londry FA. 2003. Resonant excitation in a low-pressure linear ion trap. J Am Soc Mass Spectrom 14:622–634.

Collings BA, Sudakov M, Londry FA. 2002. Resonance shifts in excitation of the $n = 0$, $K = 1$ to 6 quadrupolar resonances for ions confined in a linear ion trap. J Am Soc Mass Spectrom 13:577–586.

Collings BA, Douglas DJ. 2000. Observation of higher order quadrupole excitation frequencies in a linear ion trap. J Am Soc Mass Spectrom 11:1016–1022.

Collings BA, Campbell JM, Mao D, Douglas DJ. 2001. A combined linear ion trap time-of-flight system with improved performance and MS[n] capabilities. Rapid Commun Mass Spectrom 15:1777–1795.

Cousins LM, Thomson BA. 2002. MS[3] using the collision cell of a tandem mass spectrometer system. Rapid Commun Mass Spectrom 16:1023–1034.

Dawson PH. 1980. Ion optical properties of quadrupole mass filters. Adv Electron Electron Opt 53:153–208.

Dawson PH. 1995. Quadrupole mass spectrometry and its applications. Woodbury: AIP Press.

Dawson PH, Whetton NR. 1969. Nonlinear resonances in quadrupole mass spectrometers due to imperfect fields. Int J Mass Spectrom Ion Proc 3:1–12.

Deutch BU, Jacobsen FM, Andersen LH, Hvelplund P, Knudsen H, Holzscheiter MH, Charlton M, Laricchia G. 1988. Antihydrogen production by positronium-antiproton collisions in an ion trap. Physica Scripta T22:248–255.

Ding C, Konenkov NV, Douglas DJ. 2003. Quadrupole mass filters with octopole fields. Rapid Commun Mass Spectrom 17:2495–2502.

Dodonov A, Kozlovsky V, Loboda A, Raznikov V, Sulimenkov I, Tolmachev A, Kraft A, Wollnik H. 1997. A new technique for decomposition of selected ions in molecule ion reactor coupled with ortho-time-of-flight mass spectrometry. Rapid Commun Mass Spectrom 11:1649–1656.

Dolnikowski GG, Kristo MJ, Enke CG, Watson JT. 1988. Ion-trapping technique for ion/molecule reaction studies in the center quadrupole of a triple quadrupole mass spectrometer. Int J Mass Spectrom Ion Proc 82:1–15.

Doroshenko VM, Cotter RJ. 1996. Advanced stored waveform inverse Fourier transform technique for a matrix-assisted laser desorption/ionization quadrupole ion trap mass spectrometer. Rapid Commun Mass Spectrom 10:65–73.

Doroshenko VM, Cotter RJ. 1998. A quadrupole ion trap/time-of-flight mass spectrometer with a parabolic reflectron. J Mass Spectrom 33:305–308.

Douglas DJ. 1993. Multipole inlet systems for ion traps. US Patent 5,179,278.

Douglas DJ, Campbell JM, Collings BA. 2000. Method and apparatus for multiple stages of mass spectrometry. PCT: WO 00/33350.

Douglas DJ, French JB. 1992. Collisional focusing effects in radio frequency quadrupoles. J Am Soc Mass Spectrom 3:398–408.

Douglas DJ, Konenkov NV. 2002. Influence of the 6th and 10th spatial harmonics on the peak shape of a quadrupole mass filter with round rods. Rapid Commun Mass Spectrom 16:1425–1431.

Drees J, Paul W. 1964. Beschleunigung van elektonen in einem plasmabetatron. Z Phys 180:340–361.

Dresch T, Gulcicek EE, Whitehouse CM. 1997. Ion storage time-of-flight mass spectrometer. US Patent 5,689,111.

Everdij JJ, Huijser A, Verster NF. 1973. Improved space focusing of polar diatomic molecules in a system of quadrupole and hexapole fields. Rev Sci Instr 44:721–725.

Feynman RP, Leighton RB, Sands M. 1963. The Feynman Lectures on Physics V2: The electromagnetic field. Reading: Addison-Wesley. p. 7-2 to 7-5.

Frank AJ, Douglas DJ. 2003. Evaluation of a linear quadrupole ion trap with added octopole fields combined with time of flight mass spectrometry. Presented at the 51st ASMS Conference on Mass Spectrometry and Allied Topics, Montreal.

Franzen J. 1998. Method and device for orthogonal ion injection into a time-of-flight mass spectrometer. US patent 5,763,878.

Franzen J, Gabling R-H, Schubert M, Wang Y. 1995. Nonlinear ion traps. In: March RE, Todd JFJ, editors. Practical aspects

of ion trap mass spectrometry, Vol. 1. Boca Raton: CRC Press. pp 49–167.

Freitas MS, Marshall AG. 1999. Rate and extent of gas phase hydrogen/deuterium exchange of bradykinin ions: Evidence for peptide zwitterions in the gas phase. Int J Mass Spectrom 182(183):221–231.

Gerlich D. 1992. Advances in chemical physics LXXXII. Inhomogeneous RF fields: A versatile tool for the study of processes with slow ions. New York: John Wiley and Sons. pp 1–176.

Goeringer DE, Asano KG, McLuckey SA, Hoekman D, Stiller SW. 1994. Filtered noise field signals for mass-selective accumulation of externally formed ions in a quadrupole ion trap. Anal Chem 66:313–318.

Griffey R, Hofstadler S. 2000. Methods and apparatus for external accumulation and photodissociation of ions prior to mass spectrometric analysis. PCT: WO 00/43111.

Guan S, Marshall AG. 1993. Stored waveform inverse Fourier transform axial excitation/ejection for quadrupole ion trap mass spectrometry. Anal Chem 65:1288–1294.

Håkansson K, Axelsson J, Palmblad M, Håkansson P. 2000. Mechanistic studies of multipole storage assisted dissociation. J Am Soc Mass Spectrom 11:210–217.

Haag C, Szabo I. 1986a. New ion-optical devices utilizing oscillatory electric fields. II. Stability of ion motion in a two-dimensional hexapole field. Int J Mass Spectrom Ion Proc 73:237–275.

Haag C, Szabo I. 1986b. New ion-optical devices utilizing oscillatory electric fields. III. Stability of ion motion in a two-dimensional octopole field. Int J Mass Spectrom Ion Proc 13:277–294.

Hager JW. 1998. Mass spectrometry using a linear RF quadrupole ion trap with axial ion ejection. Presented at the 46th ASMS Conference on Mass Spectrometry and Allied Topics, Orlando, FL, 31 May–4 June.

Hager JW. 1999. Performance optimization and fringing field modifications of a 24-mm long RF-only quadrupole mass spectrometer. Rapid Commun Mass Spectrom 13:740–748.

Hager JW. 2001. Axial ejection in a multipole mass spectrometer. US Patent 6,177,66.

Hager JW. 2002a. A new linear ion trap mass spectrometer. Rapid Commun Mass Spectrom 16:512–526.

Hager JW. 2002b. Method of mass spectrometry to enhance separation of ions with different charges. US patent application 2002/0175279.

Hager JW. 2003a. Quadrupole mass spectrometer with ion traps to enhance sensitivity. US patent 6,504,148.

Hager JW. 2003b. Method of reducing space charge in a linear ion trap mass spectrometer. US patent application 2003/0042415.

Hardman M, Makarov AA. 2003. Interfacing the orbitrap mass analyzer to an electrospray source. Anal Chem 75:1699–1705.

Harkewicz R, Belov ME, Anderson GA, Paša-Tolić L, Masselon CD, Prior DC, Udseth HR, Smith RD. 2002. ESI-FTICR

mass spectrometry employing data-dependent external ion selection and accumulation. J Am Soc Mass Spectrom 13: 144–154.

Henry KD, McLafferty FW. 1990. Electrospray ionization with Fourier-transform mass spectrometry. Charge state assignment from resolved isotopic peaks. Org Mass Spectrom 25:490–492.

Hofstadler SA, Sannes-Lowery K, Griffey RH. 1999a. Infrared multiphoton dissociation in an external ion reservoir. Anal Chem 71:2067–2070.

Hofstadler SA, Sannes-Lowery KA, Griffey RH. 1999b. A gated-beam electrospray ionization source with an external ion reservoir. A new tool for the characterization of biomolecules using electrospray ionization mass spectrometry. Rapid Commun Mass Spectrom 13:1971–1979.

Hofstadler SA, Sannes-Lowery KA, Griffey RH. 2000. Enhanced gas-phase hydrogen-deuterium exchange of oligonucleotide and protein ions stored in an external multipole ion reservoir. J Mass Spectrom 35:62–70.

Hofstadler S, Griffey R. 2002. Methods and apparatus for external accumulation and photodissociation of ions prior to mass spectrometric analysis. US Patent 6,342,393.

Hopfgartner G, Husser C, Zell M. 2003. The rapid screening and characterization of drug metabolites using a new quadrupole-linear ion trap mass spectrometer. J Mass Spectrom 38: 138–150.

Hunter KL, McIntosh BJ. 1989. An improved model of the fringing fields of a quadrupole mass filter. Int J Mass Spectrom Ion Process 87:157–164.

Ijames CF. 1996. A proposed two dimension quadrupole/electrostatic ion trap time-of-flight mass spectrometer. Proceedings of the 44th ASMS Conf. Mass Spectrom Allied Topics, Portland, Oregon, 795 p.

Juhasz P, Vestal ML, Martin SA. 1997. On the initial velocity of ions generated by matrix-assisted laser desorption ionization and its effect on the calibration of delayed extraction time-of-flight mass spectra. J Am Soc Mass Spectrom 8:209–217.

Julian RK, Jr., Cooks RG. 1993. Broad-band excitation in the quadrupole ion trap mass spectrometer using shaped pulses created with the inverse Fourier transform. Anal Chem 65: 1827–1833.

Kellerbauer A, Bollen G, Dilling J, Henry S, Herfurth F, Kluge HJ, Lamour E, Moore RB, Scheidenberger C, Schwarz S, Sikler G, Szerypo J. 2002. A linear radiofrequency quadrupole ion trap for the cooling and bunching of radioactive ion beams. Nucl Phys A 701:565C–569C.

Kip AF. 1969. Fundamentals of electricity and magnetism. New York: McGraw-Hill.

Korner R, Wilm M, Morand K, Schubert M, Mann M. 1996. Nano electrospray combined with a quadrupole ion trap for the analysis of peptides and protein digests. J Am Soc Mass Spectrom 7:150–156.

Lammert SA, Plass WR, Thompson CV, Wise MB. 2000. Design, optimization and initial performance of a toroidal rf ion trap mass spectrometer. Int J Mass Spectrom 212:25–40.

Landau LD, Lifshitz EM. 1960. Mechanics, 3rd edition. New York: Pergamon Press.

Langmuir RV. 1967. Quadrupole mass filter with means to generate a noise spectrum exclusive of the resonant frequency of the desired ions to deflect stable ions. US Patent 3,334,225.

Leblanc JCY, Hager JW, Ilisiu AMP, Hunter C, Zhon F, Chu I. 2003. Unique scanning capabilities of a new linear ion trap mass spectrometer (Q TRAP) used for high sensitivity proteomics applications. Proteomics 3:859–869.

Li L, Purves RW. 1995. Development of an ion trap linear time-of-flight mass spectrometer with electrospray ionization for micro-column liquid chromatography detection. J Micro-column Separations 7:603–610.

Louris JN, Taylor DM. 1994. Method and apparatus for ejecting unwanted ions in an ion trap mass spectrometer. US Patent 5,324,939.

Louris JN, Broadbelt-Lustig JS, Cooks RG, Glish GL, Berkel GJV, McLuckey SA. 1990. Ion isolation and sequential stages of mass spectrometry in a quadrupole ion trap mass spectrometer. Int J Mass Spectrom Ion Processes 96:117–137.

Makarov AA. 2000. Electrostatic axially harmonic orbital trapping: A high-performance technique of mass analysis. Anal Chem 72:1156–1162.

Mao D, Ding C, Douglas DJ. 2002. Hydrogen/deuterium exchange of myoglobin ions in a linear quadrupole ion trap. Rapid Commun Mass Spectrom 16:1941–1945.

Mao D, Douglas DJ. 2003. H/D exchange of gas phase bradykinin ions in a linear quadrupole ion trap. J Am Soc Mass Spectrom 14:85–94.

Mao D, Babu KR, Chen Y-L, Douglas DJ. 2003. Conformations of gas-phase lysozyme ions produced from two different solution conformations. Anal Chem 75:1325–1330.

March RE, Hughes RJ. 1989. Quadrupole storage mass spectrometry. New York: John Wiley.

Marshall AG, Wang T-CL, Ricca TL. 1985. Tailored excitation for Fourier transform ion cyclotron mass spectrometry. J Am Chem Soc 107:7893–7895.

Maziarz EP III, Baker GA, Lorenz SA, Wood TD. 1999. External ion accumulation of low molecular weight poly(ethylene glycol) by electrospray ionization Fourier transform mass spectrometry. J Am Soc Mass Spectrom 10:1298–1304.

McDonnell LA, Giannakopulos AE, Derrick PJ, Tsybin YO, Håkansson P. 2002. A theoretical investigation of the kinetic energy of ions trapped in a radio-frequency hexapole ion trap. Eur J Mass Spectrom 8:181–189.

McIntosh BJ, Hunter KL. 1989. Influence of realistic fringing fields on the acceptance of a quadrupole mass filter. Int J Mass Spectrom Ion Process 87:165–179.

Micheal SM, Chien M, Lubman DM. 1992. An ion trap storage/time-of-flight mass spectrometer. Rev Sci Instrum 63:4277–4284.

Micheal SM, Chien BM, Lubman DM. 1993. Detection of electrospray ionization using a quadrupole ion trap storage/

reflectron time-of-flight mass spectrometer. Anal Chem 65:2614–2620.

Mordehai AV, Henion JD. 1993. Computer-designed waveform technique for reducing chemical noise in atmospheric-pressure ionization/ion-trap mass spectrometry. Rapid Commun Mass Spectrom 7:1131–1135.

Neushauser W, Hohenstatt M, Toschek P, Dehmelt H. 1978. Optical sideband cooling of visible atom cloud confined in a parabolic well. Phys Rev Lett 41:233–236.

Paša-Tolić L, Harkewicz R, Anderson GA, Tolić N, Shen Y, Zhao R, Thrall B, Masselon C, Smith RD. 2002. Increased proteome coverage for quantitative peptide abundance measurements based upon high performance separations and DREAMS FTICR MS. J Am Soc Mass Spectrom 13:954–963.

Paul W, Reinhard HP, von Zahn U. 1958. Das elektrische massenfilter als massenspektrometer und isotopentrenner. Z Phys 152:145–182.

Pope RM, Shen N, Nicoll J, Tarnawiecki B, Dejsupa C, Dearden DV. 1997. Gas phase salt clusters from electrosprayed alkaline earth colloids. Int J Mass Spectrom Ion Proc 162:107–119.

Prestage JD, Dick GJ, Malecki L. 1989. New ion trap for frequency standard applications. J Appl Phys 66:1013–1017.

Purves RW, Li L. 1997. Development and characterization of an electrospray ionization ion trap/linear time-of-flight mass spectrometer. J Am Soc Mass Spectrom 8:1085–1093.

Rama Rao VVK, Bhutani A. 2000. Electric hexapoles and octopoles with optimized circular section rods. Int J Mass Spectrom 202:31–36.

Rama Rao VVK, Bhutani A. 2001. Erratum to "Electric hexapoles and octopoles with optimized circular section rods" by V. V. K. Rama Rao and Amit Bhutani (Int J Mass Spectrom 202:31–36. 2001). Int J Mass Spectrom 208:249.

Raznikov VV, Soulimenkov IV, Kozlovski VI, Pikhtelev AR, Raznikova MO, Horwath T, Kholomeev AA, Zhou Z, Wollnik H, Dodonov AF. 2001. Ion rotating motion in a gas-filled radio-frequency quadrupole ion guide as a new technique for structural and kinetic investigation of ions. Rapid Commun Mass Spectrom 15:1912–1921.

Sannes-Lowery KA, Hofstadler SA. 2000. Characterization of multipole storage assisted dissociation: Implications for electrospray ionization mass spectrometry characterization of biomolecules. J Am Soc Mass Spectrom 11:1–9.

Sannes-Lowery K, Griffey RH, Kruppa GH, Speir JP, Hofstadler SA. 1998. Multipole storage assisted dissociation, a novel in-source dissociation technique for electrospray ionization generated ions. Rapid Commun Mass Spectrom 12:1957–1961.

Schwartz JC, Schey KL, Cooks RG. 1990. A penta-quadrupole instrument for reaction intermediate scans and other MS-MS-MS experiments. Int J Mass Spectrom Ion Proc 101:1–20.

Schwartz JC, Senko MW, Syka JEP. 2002a. A two-dimensional quadrupole ion trap mass spectrometer. 50th ASMS Conf. Mass Spectrom. Allied Topics, Orlando, Florida.

Schwartz JC, Senko MW, Syka JEP. 2002b. A two-dimensional quadrupole ion trap mass spectrometer. J Am Soc Mass Spectrom 13:659–669.

Senko M. 2002. Linear quadrupole mass spectrometer. US Patent 6,403,955.

Senko MW, Schwartz JC. 2002. Trapping efficiency measurements in a 2D ion trap mass spectrometer. 50th ASMS Conf Mass Spectrom Allied Topics, Orlando, Florida.

Senko MW, Hendrickson CL, Emmett MR, Shi S D-H, Marshall AG. 1997. External accumulation of ions for enhanced electrospray ionization Fourier transform ion cyclotron resonance mass spectrometry. J Am Soc Mass Spectrom 8:970–976.

Senko MW, Schwartz JC, Schoen AE, Syka JEP. 2000. Fourier transform mass spectrometry in a linear quadrupole ion trap. 48th ASMS Conf Mass Spectrom Allied Topics, Long Beach, California.

Sevugarajan S, Menon AG. 2000. Frequency perturbation in nonlinear Paul traps: A simulation study of the effect of geometric aberration, space charge, dipolar excitation, and damping on ion axial secular frequency. Int J Mass Spectrom 197:263–278.

Smythe WR. 1939. Static and dynamic electricity. New York: McGraw-Hill Book Company.

Stafford GC, Jr., Kelley PE, Syka JEP, Reynolds WE, Todd JFJ. 1984. Recent improvements in and analytical applications of advanced ion trap technology. Int J Mass Spectrom Ion Proc 60:85–98.

Suckau D, Shi Y, Beu SC, Senko MW, Quinn JP, Wampler FM, McLafferty FW. 1993. Coexisting stable conformations of gaseous protein ions. Proc Natl Acad Sci USA 90:790–793.

Sudakov M. 2001. Effective potential and the ion axial beat motion near the boundary of the first stable region in a nonlinear ion trap. Int J Mass Spectrom 206:27–43.

Sudakov M, Douglas DJ. 2003. Linear quadrupoles with added octopole fields. Rapid Commun Mass Spectrom 17:2290–2294.

Sudakov M, Konenkov N, Douglas DJ, Glebova T. 2000. Excitation frequencies of ions confined in a quadrupole field with quadrupole excitation. J Am Soc Mass Spectrom 11:10–18.

Szabo I. 1986. New ion-optical devices utilizing oscillatory electric fields. I. Principle of operation and analytical theory of multipole devices with two-dimensional electric fields. Int J Mass Spectrom Ion Proc 73:197–235.

Szilagi M. 1988. Electron and ion optics. New York: Plenum Press. p. 62.

Tanner SD, Baranov VI, Bandura DR. 2002. Reaction cells and collision cells for ICP-MS: A tutorial review. Spectrochimica Acta 57B:1361–1452.

Tolmachev AV, Udseth HR, Smith RD. 2000. Radial stratification of ions as a function of mass to charge ratio in collisional

cooling radio frequency multipoles used as ion guides or ion traps. Rapid Commun Mass Spectrom 14:1907–1913.

Voyksner RD, Lee H. 1999. Investigating the use of an octupole ion guide for ion storage and high-pass mass filtering to improve the quantitative performance of electrospray ion trap mass spectrometry. Rapid Commun Mass Spectrom 13:1427–1437.

Waki I, Kassner S, Birkl G, Walther H. 1992. Observation of ordered structures of laser cooled ions in a quadrupole storage ring. Phys Rev Lett 68:2007–2010.

Wang Y, Park MA, Giessmann UP. 2002. Apparatus and method for analyzing samples in a dual ion trap mass spectrometer. US patent: Pub. No. 2002/0121594.

Wang Y, Shi SD-H, Hendrickson CL, Marshall AG. 2000. Mass-selective ion accumulation and fragmentation in a linear octopole ion trap external to a Fourier transform ion cyclotron resonance mass spectrometer. Int J Mass Spectrom 198:113–120.

Wang Y, Park MA, Giessmann UP, Laukien F. 2001. Dual trap Q-Q-time-of-flight mass spectrometry. Proc 49th ASMS Conf Mass Spectrom Allied Topics, Chicago, Illinois.

Wang Y, Park MA, Knudsen TP, Giessmann UP, Laukien FH. 2002. Simultaneously using a segmented linear quadrupole

as a collision cell and an ion trap in a dual trap Q-q-time-of-flight mass spectrometer. Proc 50th ASMS Conf Mass Spectrom Allied Topics, Orlando, Florida.

Wells G, Huston C. 1995. Field-modulated selective ion storage in a quadrupole ion trap. J Am Soc Mass Spectrom 6:928–935.

Whitehouse CM, Andrien BA, Gulcicek EE. 1999. Mass spectrometry with multipole ion guides. PCT: WO 99/62101.

Whitehouse CM, Dresch T, Andrien BA. 1998. Multipole ion guide ion trap mass spectrometry. PCT: WO 98/06481.

Whitehouse CM, Dresch T, Andrien BA. 2000. Multipole ion guide ion trap spectrometry with MS/MSn analysis. US patent. 6,011,259.

Wilcox BE, Hendrickson CL, Marshall AG. 2002. Improved ion extraction from a linear octopole ion trap: SIMION analysis and experimental demonstration. J Am Soc Mass Spectrom 13:1304–1312.

Witt M, Fuchser J, Baykut G. 2002. In-source H/D exchange and ion-molecule reactions using matrix assisted laser desorption/ionization Fourier transform ion cyclotron resonance mass spectrometry with pulsed collision and reaction gases. J Am Soc Mass Spectrom 13:308–317.

Donald Douglas received his BSc from McMaster University in 1971, and his PhD from the University of Toronto in 1976. Following 2 years as a postdoctoral fellow at the University of California Berkeley, and a year in Ottawa at the National Research Council of Canada, he joined SCIEX as a research scientist. In 1995, he joined the Department of Chemistry of the University of British Columbia as Chairholder of the NSERC-SCIEX Industrial Chair in Scientific Instrumentation. His research interests include the structures of gas phase ions of biological molecules and new instrumentation for mass spectrometry.

Aaron Frank graduated from The College of Wooster in 1994 and earned his PhD from the University of Washington in 2000. He had postdoctoral appointments at Cornell University and the University of British Columbia. At UBC, he was involved with the construction and evaluation of linear ion trap mass spectrometers. In 2003, he joined the Analytical Chemistry group in the Chemical and Environmental Technologies division at Battelle Memorial Institute.

Dunmin Mao received his BSc in 1988 and MSc in 1992 from Fudan University in P.R. China. He received his PhD from the University of Western Ontario in 1999. For the following 4 years, he joined the group of Dr. Don Douglas at the University of British Columbia, first as a postdoctoral fellow in 2000 and then as a research associate in 2003. His research interests during that period included development of linear ion traps and the application of a linear ion trap/time-of-flight mass spectrometer to study the conformations of gas phase protein ions. He joined Covance as a scientist in 2003 specializing in method development using LC/MS/MS.

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PATENT & TRADEMARK OFFICE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : John E. P. Syka

Serial No. : 10/764,435

Filed   : 1/23/2004

Docket No.: 12671-042001
         (1021US/NAT)

Title   : Confining Positive and Negative Ions With Fast Oscillating Potentials

Art Unit   : 2881

Examiner : Paul M. Gurzo

Conf. No. : 6074

DECLARATION UNDER 37 C.F.R. §1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, John E.P. Syka, hereby declare as follows:

1. I received my B.S. degree in Electrical Engineering and Mechanical Engineering (double major) from Stanford University in 1981. I am currently a Ph.D. candidate in the Engineering Physics Graduate Program at the University of Virginia. My dissertation projects involve the conception and demonstration of a hybrid two-dimensional radio frequency (RF) quadrupole ion trap /Fourier transform ion cyclotron resonance mass spectrometer, as well as the development of a two-dimensional radio-frequency (RF) quadrupole mass spectrometer for ion/ion reaction experiments, with which we have demonstrated a new dissociation method (electron transfer dissociation) for peptide ions. I expect to complete the requirements for my Ph.D. degree by the end of 2005.

2. I have over twenty years of employment experience in the mass spectrometry industry. I worked for Finnigan Instruments Corporation during the summers of 1978-1980 as a technician/assistant in its research department. After graduating from Stanford in 1981, I joined Finnigan MAT (Finnigan Instruments' successor)

App. Serial No. 10/764,435

as a full-time research employee, and have remained as an employee of Finnigan MAT and its successor entities (currently Thermo Finnigan LLC, a subsidiary of Thermo Electron Corporation) until the present. My primary responsibilities have involved designing and developing novel mass spectrometers and mass spectrometer subsystems and conducting related research. I have participated in the design and development of numerous commercial mass spectrometer systems, including quadrupole mass filter spectrometers and two-dimensional and three-dimensional ion trap mass spectrometers.

3. In the course of performing my duties, I have materially contributed to a number of significant advances in mass spectrometry technology, including the development and characterization of the mass selective instability scan for ion trap mass spectrometers, and the design and development of a radial-ejection two-dimensional ion trap that is currently used in several of Thermo Finnigan's commercial products. In 2004, I was awarded a technical innovation award by Thermo Finnigan in recognition of my contributions.

4. I have co-authored 18 articles published in the scientific and technical literature relating to mass spectrometry, and have made numerous oral and poster presentations at scientific conferences. I am a named inventor on 12 issued U.S. patents and 4 pending U.S. patent applications (including the above-identified Application), the vast majority of which relate to improvements in ion trap mass spectrometers.

5. Through my professional and educational experience, I have acquired specific expertise in the following areas:

- The physics of ion motion in RF quadruple fields and RF multipole field devices;
- Electronics for RF quadrupole field devices;
- Mechanical fabrication of RF quadrupole analyzers; and

2

App. Serial No. 10/764,435

- The design of RF quadrupole field mass spectrometer systems.

I am closely familiar with the terminology customarily used by persons skilled in these areas, and in the ion trap mass spectrometry field in general.

6. Each of the independent claims of the present Application recites steps of or apparatus for axial confinement of ions within an ion channel of an ion trap or guide. In particular, claim 1 recites a step of "applying periodic voltages to electrodes in the second set of electrodes to generate a second oscillating electric potential that axially confines the ions in the ion channel." Similarly, claim 17 recites "a controller configured to apply periodic voltages to electrodes in the first set and the second set to establish a first oscillating electric potential and a second oscillating electric potential, wherein the first and second oscillating electric potentials have different spatial distributions and confine ions in the ion channel in radial and axial directions, respectively." The terms "axially" and "axial" have customary meanings that are well established in the ion trap mass spectrometry art to which the present Application pertains. The electric fields and ion motion within ion traps are customarily characterized in terms of an axial dimension and one or more radial dimensions orthogonal to the axial dimension. The term "axially confined" signifies that the movement of ions is restricted in the axial dimension. As applied to conventional two-dimensional quadrupole ion trap devices (commonly referred to as "linear ion traps"), "axially" or "axial" refer to the central longitudinal axis of the trap extending between the ends of the device, and "axially confining" ions means constraining the ions' movement in the dimension defined by the central longitudinal axis such that the ions remain within the trap or a section thereof. In this context, axial confinement is different than and distinguishable from radial confinement (as that term would be understood by persons skilled in the art), which means constraining the ions' movement in the dimensions orthogonal to the axis of elongation such that the ions do not strike the electrodes and/or escape the trap or guide through the gaps between electrodes.

3

App. Serial No. 10/764,435

7. I have reviewed the Office Action dated September 8, 2005 relating to the present Application, in which the Examiner rejected certain claims as being unpatentable over U.S. Patent No. 5,089,703 to Schoen et al. (the '703 Patent). I am a named co-inventor on the '703 Patent and consequently have a thorough knowledge of its teachings. The '703 Patent discloses a method and apparatus for improving resolution in a RF quadrupole mass filter-type mass spectrometer by applying a supplemental RF field that resonantly renders ions unstable. Roughly described, a beam of ions is projected axially (i.e., along the longitudinal axis) into an entrance end of a quadrupole mass filter. Ions having mass-to-charge ratios (m/z's) within selected ranges traverse the entire length of the quadrupole structure and emerge via an exit end thereof. A detector may be placed proximate the exit end to detect and measure the transmitted ions. Ions having m/z's outside of the selected ranges become radially unstable within the quadrupole filter, and either strike the electrode surfaces or escape through the inter-electrode gaps. Sharpening of the m/z dependence of transition between ion transmission and rejection ions is enhanced by means of a supplemental RF field applied throughout the device having at least one frequency that matches a characteristic frequency of motion of an undesired ion. In a preferred embodiment, the frequency of the supplemental field is modulated so as to modulate the transmission of ions of m/z near this transmission and rejection boundary. The modulated ion signal is selectively detected and demodulated to provide an m/z signal of improved resolution.

8. The '703 Patent does not teach or suggest axial confinement of ions in an ion channel, because the motion of ions along the central longitudinal axis of the quadrupole mass filter is not constrained or impeded by the application of the primary or supplemental RF voltages. In fact, the detected ions must traverse the entire length of the mass filter and exit its terminal end. Those ions that do not transmit axially though the mass filter are radially ejected from the mass filter and not retained in the device. This constitutes the essential operating principle of the invention embodied in the '703 Patent.
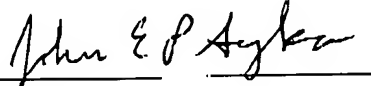
4

App. Serial No. 10/764,435

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. §1001 and that such willful false statements may jeopardize the validity of the Application or any patent issued thereon.

Dated: _10/19/2005_

John E. P. Syka
John E/P. Syka

5